11/25 left voice mail. 1:15 pm

Access DB# 108741

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jeoyuh Lin Examiner #: 77403 Date: 11/20/03
Art Unit: _____ Phone Number 30 605990 Serial Number: 09/706,584
Mail Box and Bldg/Room Location: CP2 4C04 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Method and devices for Heart treatment

Inventors (please provide full names): Richard L. Mueller ; U. Hiram Chee

Earliest Priority Filing Date: 11/5/99

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Search for method of treating ischemia
- imaging heart → Finding
  - Various modality
  - Source of oxygenated blood source
  - Area with underperfused region
  - Tissue between oxygenated source & under pertyed region.
- Introduce stimulus to promote angiogenis (blood capillary vessel growth) from oxygenated blood source - underpertused region
  - Injury, growth factor, protein
- Sustaining blood supply. ie, injury by piercing, heating, etc.
  - exercise
  - demand for

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: J Sims	NA Sequence (#) _____	STN ✓
Searcher Phone #: 308-4836	AA Sequence (#) _____	Dialog ✓
Searcher Location: EIC 3700	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: 11/28/03	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: _____	Other _____	Other (specify) _____

PTO-1590 (8-01)

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 144

Therapeutic angiogenesis **in critical limb and myocardial ischemia**

...in animal models of ischemia has shown that administration of angiogenic growth factors, either as a recombinant protein or by gene transfer, can augment nutrient **perfusion** through neovascularization to **promote** the development of supplemental collateral blood vessels that will constitute endogenous bypass conduits around occluded native arteries; a strategy termed "therapeutic **angiogenesis** ". In animal models and clinical trials, the best studied cytokines with angiogenic activity are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of therapeutic **angiogenesis** in patients with critical limb ischemia demonstrated resolution of rest pain and/or improved limb integrity, increased pain-free walking time and ankle-brachial index...

...magnetic resonance imaging. Initial clinical trials in patients with end-stage coronary artery disease using direct myocardial injection via thoracotomy resulted in large increases in **exercise** time and marked reductions in anginal symptoms, as well as objective evidence of improved **perfusion** and left ventricular function. Larger scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein, and have not shown significant improvement in **exercise** time or angina compared to placebo. Larger scale placebo-controlled studies of gene transfer using catheter-based endocardial delivery are in progress. Future clinical studies...

...administration, and combinations of growth factors, as well as the requirement for endothelial progenitor cell or stem cell supplementation, to provide effective and safe therapeutic **angiogenesis** for patients with critical limb ischemia and chronic myocardial ischemia who are not candidates for conventional revascularization procedures.
MEDICAL DESCRIPTORS:
...*limb ischemia--therapy--th; *heart muscle ischemia--diagnosis--di; * heart muscle ischemia--drug therapy--dt; *heart muscle ischemia--etiology --et; *heart muscle ischemia--therapy--th; * **angiogenesis** ; *endothelium cell; *cell proliferation; *smooth muscle fiber; *hypotension--side effect --si; *edema--side effect--si; *anemia--side effect--si; *thrombocytopenia --side effect--si

11/3,KWIC/10 (Item 1 from file: 155)

15738501 22979588 PMID: 14615023
Angiogenic gene therapy with adenovirus 5 fibroblast growth factor-4 (Ad5FGF-4): a new option for the treatment of coronary artery disease.
Grines Cindy; Rubanyi Gabor M; Kleiman Neal S; Marrott Pran; Watkins Matthew W
William Beaumont Hospital, Royal Oak, Michigan 48073, USA. cgrines@beumont.edu
American journal of cardiology (United States) Nov 7 2003, 92 (9B) p24N-31N, ISSN 0002-9149 Journal Code: 0207277
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process

16/3,KWIC/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

12006994 Genuine Article#: 720FC No. References: 17
Title: Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged, submaximal exercise **in humans**
Author(s): Hiscock N; Fischer CP; Pilegaard H; Pedersen BK (REPRINT)
Corporate Source: Rigshosp,Dept Infect Dis, Copenhagen Muscle Res Ctr, Dpt 7641,Blegdamsvej 9/DK-2100 Copenhagen//Denmark/ (REPRINT); Rigshosp,Dept Infect Dis, Copenhagen Muscle Res Ctr, Dpt 7641,DK-2100 Copenhagen//Denmark/; Univ Copenhagen,August Krogh Inst,DK-2100 Copenhagen//Denmark/
Journal: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, 2003, V285, N4 (OCT), PH1759-H1763
ISSN: 0363-6135 Publication date: 20031000
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged, submaximal exercise **in humans**
Abstract: Angiogenesis, the **growth** of new **blood vessels** from existing ones, occurs in the skeletal muscle as an adaptive response to **exercise** that satisfies the increased requirement of this tissue for oxygen delivery and metabolic processes. Of the factors that have been identified to regulate this process...

...to measure the skeletal muscle VEGF mRNA content and arteriovenous protein balance across the working leg in response to a single bout of prolonged, submaximal **exercise** . Seven physically active males completed 3 h of two-legged kicking ergometry. Muscle biopsies were collected from the vastus lateralis muscle from both working legs, and blood samples were collected from one femoral artery and femoral vein before, during, and in recovery from **exercise** . We show that the **exercise** stimulus elicited a decrease in VEGF protein arteriovenous balance across the **exercising** leg (P = 0.007), and a ninefold elevation in skeletal muscle VEGF mRNA expression (P < 0.001). The changes in VEGF protein balance and mRNA content were most pronounced 1 h after the cessation of **exercise** . In conclusion, these findings demonstrate that submaximal **exercise** , suitable for humans with low CV fitness, induces a decrease in VEGF arteriovenous balance that is likely to be of clinical significance in **promoting** angiogenic effects.

16/3,KWIC/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04470799 Genuine Article#: TF258 No. References: 32
Title: VEGF GENE-EXPRESSION IS UP-REGULATED IN ELECTRICALLY STIMULATED RAT SKELETAL-MUSCLE
Author(s): HANG J; KONG L; GU JW; ADAIR TH
Corporate Source: UNIV MISSISSIPPI,MED CTR,DEPT PHYSIOL & BIOPHYS,2500 N STATE ST/JACKSON//MS/39216; UNIV MISSISSIPPI,MED CTR,DEPT PHYSIOL & BIOPHYS/JACKSON//MS/39216; UNIV MISSISSIPPI,MED CTR,DEPT MICROBIOL/JACKSON//MS/39216
Journal: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, 1995, V38, N5 (NOV), PH1827-H1831

ISSN: 0363-6135
Language: ENGLISH Document Type: NOTE (Abstract Available)

...Abstract: purpose of this study was to determine whether VEGF gene expression is upregulated in chronically stimulated skeletal muscles, where hypoxia is thought to trigger the **growth** of **blood vessels** . The right anterior tibialis and extensor digitorum longus muscles of 12 rats were stimulated electrically (10 Hz, 300 mu s pulses) for up to 21 ...

...are consistent with a metabolic hypothesis in which tissue oxygenation controls VEGF expression. These studies support the hypothesis that VEGF has a physiological role in **promoting** angiogenesis in stimulated skeletal muscle.
?

John Sims EIC 3700 308-4836

19/3,KWIC/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10367485 Genuine Article#: 518HF No. References: 26
Title: Therapeutic angiogenesis **for critical limb ischemia: invited commentary**
Author(s): Messina LM (REPRINT) ; Brevetti LS; Chang DS; Paek R; Sarkar R
Corporate Source: Univ Calif San Francisco M488,Dept Surg, Div Vasc Surg,505 Parnassus Ave/San Francisco//CA/94143 (REPRINT); Univ Calif San Francisco M488,Dept Surg, Div Vasc Surg,San Francisco//CA/94143
Journal: JOURNAL OF CONTROLLED RELEASE, 2002, V78, N1-3 (JAN 17), P285-294
ISSN: 0168-3659 Publication date: 20020117
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Therapeutic angiogenesis **for critical limb ischemia: invited commentary**
...Abstract: occlusive disease results in tissue ischemia of the legs and is relatively common in the elderly. Clinically, it may be asymptomatic, cause muscle pain during **exercise** , or progress to a severe degree of ischemia that may result in limb loss. Although bypass surgery, and angioplasty have increased the rate of limb salvage in these patients, amputation of the affected limb remains a common outcome for many patients. Therapeutic **angiogenesis** is the administration of angiogenic factors, or genes encoding these factors, to **promote** neovascularization and thereby increase blood flow to the ischemic leg. We have developed an animal model of hindlimb ischemia in which to study therapeutic **angiogenesis** . We chose nitric oxide as the angiogenic factor for our experiments because of its ability to induce **angiogenesis** , vasodilation, and inhibit inflammation. In this review, we will discuss our experience with our model of hindlimb ischemia, as well as discuss our results of gene therapy for therapeutic **angiogenesis** using nitric oxide. (C) 2002 Published by Elsevier Science B.V.
...Identifiers--ENDOTHELIAL GROWTH-FACTOR; INTRAMUSCULAR GENE-TRANSFER; BLOOD-FLOW; RABBIT MODEL; IN-VIVO; RAT; HINDLIMB; PROLIFERATION; EXPRESSION; **PERFUSION**

19/3,KWIC/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07906752 Genuine Article#: 222HV No. References: 23
Title: Heparin potentiates collateral growth but not growth of intramyocardial endarteries in dogs with repeated coronary occlusion
Author(s): Fujita M (REPRINT) ; Kihara Y; Hasegawa K; Nohara R; Sasayama S
Corporate Source: KYOTO UNIV,COLL MED TECHNOL, SAKYO KU, 53 KAWAHARACHO/KYOTO 606//JAPAN/ (REPRINT); KYOTO UNIV,DEPT CARDIOVASC MED, GRAD SCH MED/KYOTO 606//JAPAN/
Journal: INTERNATIONAL JOURNAL OF CARDIOLOGY, 1999, V70, N2 (JUL 31), P 165-170
ISSN: 0167-5273 Publication date: 19990731
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

...Abstract: beneficial effect of heparin on canine collateral development. Seventeen adult mongrel dogs were instrumented for measurements of a

subendocardial segment length in the central area **perfused** by the left circumflex coronary artery, its flow, and left ventricular pressure. A pulsed Doppler flow probe and an externally inflatable pneumatic occluder were placed...

...neovascularization toward the ischemic area) was comparable in dogs with and without heparin (15.4+/-12.4% vs. 21.1+/-13.6%, p=NS). Heparin **promotes** nonsprouting **angiogenesis** (arteriogenesis) of preformed collateral vessels but not neovascularization toward the ischemic area in dogs with brief repetitive coronary occlusions. (C) 1999 Elsevier Science Ireland Ltd...

...Identifiers--REGIONAL MYOCARDIAL-FUNCTION; MOLECULAR-WEIGHT HEPARIN; STABLE-EFFORT ANGINA; TREADMILL CAPACITY; CONSCIOUS DOGS; ARTERY DISEASE; CANINE MODEL; DOUBLE-BLIND; **EXERCISE;** PRETREATMENT

19/3,KWIC/3 (Item 3 from file: 34)

05709623 Genuine Article#: WR446 No. References: 15

Title: Effect of basic fibroblast growth factor on myocardial angiogenesis **ins dogs with mature collateral vessels**

Author(s): Shou M; Thirumurti V; Rajanayagam S; Lazarous DF; Hodge E; Stiber JA; Pettiford M; Elliott E; Shah SM; Unger EF (REPRINT)
Corporate Source: NHLBI,PHYSL & PHARMACOL SECT, CARDIOL BRANCH, NIH, BLDG 10, ROOM 7B15, 10 CTR DR /BETHESDA//MD/20892 (REPRINT); NHLBI,PHYSL & PHARMACOL SECT, CARDIOL BRANCH, NIH/BETHESDA//MD/20892

Journal: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 1997, V29, N5 (APR) , P1102-1106
ISSN: 0735-1097 Publication date: 19970400
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Effect of basic fibroblast growth factor on myocardial angiogenesis **ins dogs with mature collateral vessels**

Abstract: Objectives. We sought to evaluate the potential of basic fibroblast growth factor (bFGF) to enhance coronary collateral **perfusion** in dogs with chronic single-vessel coronary occlusion. A secondary goal was to examine whether the salutary effects of bFGF treatment, previously proved effective in...

...bFGF, an angiogenic growth factor, is currently the subject of a Phase I trial in patients with ischemic heart disease. It has been shown to **promote** collateral development in dogs with progressive coronary occlusion when given during the period of natural collateralization. The effect of bFGF on quiescent collateral vessels, a...

...circumflex coronary artery and randomized to bFGF (1.74 mg/day for 7 days), a regimen previously proved effective, or to saline solution. Maximal collateral **perfusion** was assessed 6 months later, and the dogs were reassigned to a course of bFGF or saline solution. Collateral **perfusion** was reevaluated after the second treatment course.

Results. At 6 months, collateral function was identical in the groups treated initially with bFGF and saline solution...

...Identifiers--BLOOD-FLOW MEASUREMENTS; CORONARY-ARTERY; HEPARIN; **EXERCISE**

Research Fronts: 95-2892 001 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; TUMOR **ANGIOGENESIS** ; COORDINATE EXPRESSION)

John Sims EIC 3700 308-4836

95-3557 001 (CEREBRAL BLOOD-FLOW DURING CARDIOPULMONARY BYPASS; REGIONAL VASCULAR RESERVE; FETAL SHEEP; MYOCARDIAL HEMATOCRIT GRADIENT; DIABETIC RATS)

19/3,KWIC/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

05909883 EMBASE No: 1994315785
Clinical significance of coronary vascular adaptations to exercise **training**
McKirnan M.D.; Bloor C.M.
Department of Pathology, UCSD School of Medicine, 9500 Gilman Drive,San Diego, CA 92093-0612 United States
Medicine and Science in Sports and Exercise (MED. SCI. SPORTS EXERC.) (United States) 1994, 26/10 (1262-1268)
CODEN: MSCSB ISSN: 0195-9131
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Clinical significance of coronary vascular adaptations to exercise **training**

Coronary vascular adaptations to **exercise** training have been extensively studied at the microscopic level in animals and correlated with direct and indirect measurements of myocardial blood flow in patients with coronary artery disease. Animals have permitted more extensive study. These findings have generally supported an increased blood flow to the myocardium with **exercise** training. However, consistent positive structural and functional adaptations to training have not been observed in large animals. Clinical studies have been limited by methodological problems related to techniques for detecting ischemia and measuring myocardial blood flow and the variability in **exercise** stimulus. Well-established ischemia and high-intensity, long-duration training were the factors that **promoted** vascular growth in **exercising** patients with coronary artery disease. Animals studies also have demonstrated the necessity for myocardial ischemia to be present to induce coronary collateral development with **exercise** training. Optimal **promoters** of vascular growth in patients with coronary disease may consist of pharmacological interventions combined with **exercise** training.
MEDICAL DESCRIPTORS:
*coronary artery blood flow; *coronary artery collateral circulation; * **exercise**
adaptation; **angiogenesis** ; conference paper; heart muscle **perfusion** ; human; nonhuman

19/3,KWIC/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09468014 21241646 PMID: 11345391
Transendocardial delivery of autologous bone marrow enhances collateral perfusion **and regional function in pigs with chronic experimental myocardial ischemia.**
Fuchs S; Baffour R; Zhou Y F; Shou M; Pierre A; Tio F O; Weissman N J; Leon M B; Epstein S E; Kornowski R
Cardiovascular Research Institute, Washington Hospital Center, Washington, DC 20010, USA. sxf6@mhg.edu

John Sims EIC 3700 308-4836

Journal of the American College of Cardiology (United States) May 2001, 37 (6) p1726-32, ISSN 0735-1097 Journal Code: 8301365
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Transendocardial delivery of autologous bone marrow enhances collateral perfusion **and regional function in pigs with chronic experimental myocardial ischemia.**

OBJECTIVES: We tested the hypothesis that intramyocardial injection of autologous bone marrow (ABM) **promotes** collateral development in ischemic porcine myocardium. We also defined, in vitro, whether bone marrow (BM) cells secrete vascular endothelial growth factor (VEGF) and macrophage chemoattractant...

... MCP-1). BACKGROUND: The natural processes leading to collateral development are extremely complex, requiring multiple growth factors interacting in concert and in sequence. Because optimal **angiogenesis** may, therefore, require multiple angiogenic factors, we thought that injection of BM, which contains cells that secrete numerous angiogenic factors, might provide optimal therapeutic **angiogenesis** . METHODS: Bone marrow was cultured four weeks in vitro. Conditioned medium was assayed for VEGF and MCP-1 and was added to cultured pig aortic...

... n = 7) was injected transendocardially into the ischemic zone (0.2 ml/injection at 12 sites). Echocardiography to assess myocardial thickening and microspheres to assess **perfusion** were performed at rest and during stress. RESULTS: Vascular endothelial growth factor and MCP-1 concentrations increased in a time-related manner. The conditioned medium ...

... 37 +/- 56 during pacing, p = 0.23). CONCLUSIONS: Bone marrow cells secrete angiogenic factors that induce endothelial cell proliferation and, when injected transendocardially, augment collateral **perfusion** and myocardial function in ischemic myocardium.

; Bone Marrow Transplantation--instrumentation--IS; Cells, Cultured; Chronic Disease; Echocardiography; Endothelial Growth Factors; **Exercise** Test; Feasibility Studies; Injections--instrumentation--IS; Injections --methods--MT; Lymphokines; Monocyte Chemoattractant Protein-1; Myocardial Ischemia--pathology--PA; Myocardial Ischemia--physiopathology--PP; Myocardial Ischemia--ultrasonography...
?

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JLin

FILE 'HCAPLUS, LIFESCI, MEDICONF, RUSSCI' ENTERED AT 10:18:02 ON 28 NOV 2003

L1	73491	S	ISCHEMI?
L2	379382	S	CARDIAC? OR MYOCARD? OR HEART?
L3	135404	S	OXYGENAT? OR PERFUS? OR UNDERPERFUS?
L4	153098	S	IMAGING?
L5	249864	S	SPECT OR ((SINGLE()PHOTON()EMISSION()COMPUTED) OR (POSITRON()
L6	237	S	ECHOPLANAR? OR ECHO()PLANAR?
L7	236	S	L1 AND (L2 AND L3) AND L4
L8	94	S	L5 AND L7
L9	1	S	L6 AND L7
L10	22399	S	ANGIOGENES?
L11	9	S	(L8 OR L9) AND L10
L12	200407	S	GROWTH()FACTOR? OR RECOMBINANT()PROTEIN?
L13	1008607	S	STIMULAT? OR IRRITAT? OR INJUR?
L14	2993	S	L10 AND L12 AND L13
L15	3	S	L1 AND L2 AND (L4 OR L5) AND L14
L16	12	S	L11 OR L15
L17	11	DUP	REMOVE L16 (1 DUPLICATE REMOVED)

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? ds

Set     Items   Description
S1         93   AU='MUELLER R L'
S2         14   AU='MUELLER RICHARD L'
S3        107   S1 OR S2
S4         38   AU='CHEE U':AU='CHEE URIEL HIRAM'
S5          5   S3 AND S4
S6       4051   (CARDIAC OR HEART)(S)ISCHEM?
S7    1146862   IMAG?
S8      12030   OXYGENAT? OR PERFUS? OR UNDERPERFUS? OR UNDER()PERFUS
S9         11   UNDER()PERFUS?
S10     12030   S8 OR S9
S11      4501   ANGIOGENES?
S12       147   S6 AND S7
S13       104   S10 AND S11
S14         5   S12 AND S13
S15        10   S5 OR S14
? show files
File 347:JAPIO Oct 1976-2003/Jul(Updated 031105)
         (c) 2003 JPO & JAPIO
File 350:Derwent WPIX 1963-2003/UD,UM &UP=200376
         (c) 2003  Thomson Derwent
File 371:French Patents 1961-2002/BOPI 200209
         (c) 2002 INPI.  All rts. reserv.
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? ds

Set      Items   Description
S1       89466   ANGIOGENES?
S2     1104731   PROMOT?
S3        3012   S2(3N)S1
S4      529593   EXERCIS?
S5          11   S3(S)S4
S6      493982   PERFUS?
S7       14373   S4(S)S6
S8         115   S1 AND S7
S9          16   S2 AND S8
S10         23   S5 OR S9
S11         10   RD (unique items)
S12       4314   BLOOD(3N)VESSEL?(3N)GROWTH?
S13        384   S2(S)S12
S14          4   S4 AND S13
S15          4   S14 NOT S10
S16          2   RD (unique items)
S17         22   (S1 OR S12) AND S2 AND S4 AND S6
S18          5   S17 NOT (S10 OR S14)
S19          5   RD (unique items)
? show files
File   2:INSPEC 1969-2003/Nov W3
         (c) 2003 Institution of Electrical Engineers
File   5:Biosis Previews(R) 1969-2003/Nov W4
         (c) 2003 BIOSIS
File   6:NTIS 1964-2003/Nov W5
         (c) 2003 NTIS, Intl Cpyrght All Rights Res
File   8:Ei Compendex(R) 1970-2003/Nov W3
         (c) 2003 Elsevier Eng.  Info. Inc.
File  34:SciSearch(R) Cited Ref Sci 1990-2003/Nov W4
         (c) 2003 Inst for Sci Info
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File  73:EMBASE 1974-2003/Nov W4
         (c) 2003 Elsevier Science B.V.
File 155:MEDLINE(R) 1966-2003/Nov W4
         (c) format only 2003 The Dialog Corp.
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? ds

Set     Items   Description
S1    2895211   CARDIAC? OR MYOCARD? OR HEART?
S2     663398   ISCHEMI?
S3    1805975   IMAGING? OR SPECT OR SINGLE()PHOTON()EMISSION()COMPUTED()T-
              OMOGRAPH? OR POSITRON()EMISSION()TOMOGRAPH? OR PET OR MAGNETI-
              C()RESONANCE OR MRI
S4      12655   (ECHOPLANAR OR ECHO()PLANAR OR MYOCARDIAL()PERFUSION)()IMA-
              GING
S5    1805975   S3 OR S4
S6     295911   S1(S)S2
S7      24207   S5 AND S6
S8      89360   ANGIOGENES?
S9    3954002   STIMULAT? OR IRRITAT? OR INJUR?
S10    852878   GROWTH()FACTOR? OR RECOMBINANT()PROTEIN?
S11    609317   OXYGENAT? OR PERFUS?
S12     17916   S8 AND S9
S13        49   S7 AND S12
S14        33   S13 AND S10
S15        21   S13 AND S11
S16        38   S14:S15
S17        26   RD (unique items)
S18        49   S13
S19        29   RD (unique items)
S20        10   S19 AND PY<2000
? show files
File   2:INSPEC 1969-2003/Nov W3
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File   5:Biosis Previews(R) 1969-2003/Nov W4
         (c) 2003 BIOSIS
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         (c) 2003 NTIS, Intl Cpyrght All Rights Res
File   8:Ei Compendex(R) 1970-2003/Nov W3
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File  34:SciSearch(R) Cited Ref Sci 1990-2003/Nov W4
         (c) 2003 Inst for Sci Info
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File  73:EMBASE 1974-2003/Nov W3
         (c) 2003 Elsevier Science B.V.
File 155:MEDLINE(R) 1966-2003/Nov W3
         (c) format only 2003 The Dialog Corp.
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Case Analysis 09/706,584

Summary

The election requirement paper No. 6 was in error in that it proposed subcombinations as species and failed to require election of the bona fide method species present - alternative sustained mechanical injury device usages and alternative cell growth factor delivery vehicle usage.

The Office First Action paper No. 12 is in error in that the base reference Hammond is not anticipatory since it does not even partly reveal either identifying the target bridging area or the sustained demand steps a), c) of applicants angiogenic treatment method.

The Office first Action paper No. 12 is further in error in that the Mann in view of Pearlman rejection under 35USC103 is also improper.

The Mann reference is fairly characterizable as recognizing that both mechanical injury and cell-growth factor injection may be used synergistically to promote angiogenesis in ischemic myocardium. Otherwise Mann is similarly deficient to Hammond re steps a) and c). Pearlman, which is used to track re-perfusion at a treated myocardial site, does not supplant these teaching deficiencies in combination therewith.

The Examiner is misunderstanding the invention in this regard. It would be helpful for him to work closely with a mentor to read each claim limitation in light of the specification against the prior art and resist the tendency to dilute the literal claim language with a compromise reading in relation to cited art.

The Invention

The invention pertains to angiogenic treatment of heart ischemia where angiogenesis or the growth of new myocardial blood vessels may be induced either by angiogenic drug delivery ('drug trigger') and/or by an injury stimulus caused by delivery of an injury agent (drug or energy, termed a 'biological trigger'). First cardiac imaging is used to identify an underperfused region of the heart which is at risk is identified. Then a nearby small-vessel blood supply capable of providing perfusing blood is identified. Finally, the bridging region between this available blood source

and the underperfused area is treated with the angiogenic drug and/or with the prior delivery of an injury stimulus agent to deliberately create an injury or 'capillary blush' in the bridging region in order to induce blood delivery to the underperfused region. Once such an induction is made, "sustained demand" is used to make permanent the additional bloodflow channels so-induced, meaning that chemical or viral agents or an exercise regimen or repeat of the injury agent biological trigger is adhered to such that the augmented flow pattern is made permanent by the body. (Specification page 12 -13 bridging summarizes this.)

Formalities

Serial no. Provided spec page 14 line 2 is incorrect. Should be corrected and status updated.

The Initial Election Requirement

In consideration of the above description the species election requirement paper No. 6 was incorrect.

"Species I" - The heart exercising device of Fig. 17 is a cardiotachometer which has no species alternative to itself under the disclosure, moreover exercise is not mutually exclusive under the disclosure to the other sustained demand devices, since exercise is stated to be practiced along with sustained mechanical injury as an oxygen demand promoter(specification page 26 lines 12-16).

"Species II" - Alternative species of mechanical injury device are present and represented in the claims however a proper species election statement would announce them: --Species of alternative coring devices (as represented by Figs. 5A and 7A through 9B) themselves alternative to the differing wire injury devices (Fig. 5B and 10 - 13) themselves alternative to the different endocardial scuffing device(s) (Figs., 14 - 15). Since their selection in a given patient is specific to the site of ischemia (deep wall or surface) their usage is mutually exclusive to each other.--

"Species III" - Since both cardiac cell-growth factor stimuli and mechanical

devices are used to both stimulate and sustain angiogenesis, alone or in use together, they are not alternative to each other. Since the growth cell factors (FGF-2,FGF-1,VEGF, PDGF,IDF-1) are stated to be usable together in combination they are not mutually exlcusive under the disclosure and therefore not species, see spec page 4 lines 22 - 26. What is alternative is the installment technique by recombinant protein or vector intermediate or whole cell (myoblast) delivery vehicle. Since viral transfection (page 6 line 8) is akin to recombinant protein delivery, again it appears that cell growth factors are usable together and both as angiogenic stimuli and sustainers, and only -- Species of alternative growth factor delivery vehicles are present as represented by claims 6, 7 and 8...-- may be posed to the applicants.

"Species IV" - An angiogram pertains to x-ray fluoroscopic imaging of the condition of the heart's arteries and therefore is not the right nomenclature for the alternatives recited in the specification pages 4 lines 9 - 13 and page 11 lines 3 - 14 which both use the conventional angiogram definition. Alternative modalities of heart imaging including myocardial perfusion imaging are indeed present (MPI, SPECT, PET, ultrasound, x-ray,MRI, thallium scinitgraphy) however they may be used together and therefore are not alternative, specification page 11 line 10.Additionally, the sole claim directed to these, claim 2 is in a Markush-type format and the 'unduly burdensome' requirement of MPEP 808.01(a) where claims are generic to the species feature being elected is unmet.

The net effect now is that we are dealing with method steps to some subcombinations (cell-growth delivery stimulus steps and sustained demand exercising steps) and leaving out other subcombinations (mechanical stimulus step types -claims 10-16) and further step of second stimulus stage +imaging-claim 17) as well as omitting one of two proper species election options (Species III above as pertains to claims 6-8).

The Claim Rejections

Base claim 1 calls for 1) initial imaging to identify an available blood vessel(s) source, an underperfused ischemic areaa and a bridging therapeutic target area across which angiogenesis must be stimulated, 2) introduction of the angiogenic stimulus at plural sites within the target area, and 3) sustainment of the oxygen demand at the target area for a time sufficient to convert the created capillary network to an arterial network.

It is important to understand the three categories of cardiac muscle to which applicants refer:

Normal - well-perfused and viable

Hibernating - Specification page 9 lines 20-29; muscle which is functionally dormant but yet viable. Aslo termed ischemic/underperfused

Infarcted - No longer viable

The term 'hibernating' is well-likenable to the natural case from which the word is drawn because under chronic ischemic conditions portions of myocardium go into an under-performing sleep state identified by electrical responsiveness but kinetic sluggishness and causing effort angina, however the muscle is revivable once re-perfused.

Hence while claim 1 step b) is likenable to 'wakening the bear in mid-winter', step c) pertains to 'putting the bear on a treadmill or poking him for a sustained period so he stays awake'. Specifically, sustained oxygen demand must be caused in the treated tissue to an extent and long enough to stimulate a transition from initial generation of capillary passageways in the (disordered) myocardial sinusoids to permanent small-artery structure.

Hammond does not in any way describe this latter step c). Anticipation is predicated upon certainty where inherency is invoked; the Examiner cannot simplify the rejection burden by invoking 'inherency' to bridge an untaught teaching gap.

Hammond in fact does not teach step a) either. Since Hammond is attempting 1) direct coronary infusion (i.e at best an injection into a vessel 'proximate to a boundary of the under-perfused region') or 2) direct infusion to the under-perfused site, Hammond has no need to identify a target bridging area and therefore is not tailored to effect re-perfusion in

the bridging area but rather to cause wholesale angiogenesis by saturation infusion as per 1) or hibernation site angiogenesis by direct access puncture as per 2).
Hammond is not an anticipatory teaching.

103 Mann v Pearlman

The Mann reference exhibits the artisan's cognizance that both mechanical injury and cell growth factor infusion can act synergistically to promote angiogenesis. However Mann is similarly limited re steps a) and c) to Hammond...there is no teaching of these steps. Pearlman merely established that angiogenic re-perfusion of myocardium however promoted can be monitored via a particular MRI imaging technique and therefore does not remedy the deficiencies of Mann.
Mann v. Pearlman is not a sustainable rejection ground.

Patentability findings - Exercise has long been known to promote collateral circulation within the myocardium. It is probably a STIC search topic since for this feature standing alone (the proposal that exercise would stimulate growth of artificially induced blood vessels analogous to the way it stimulates growth of the natural myocardial vessels) would not necessarily develop through the patent literature. STIC Search

10d

Francis J. Jaworski
Primary Examiner
7-1-03

5/3/4 (Item 4 from file: 350)
DIALOG(R)File 350:Derwent WPIX

013859173 **Image available**
WPI Acc No: 2001-343386/200136
XRPX Acc No: N01-248684

Treatment method for patient with heart disorders, involves creating annulus of injury about core of healthy cells in myocardial layer of heart between underperfused region and source of oxygenated blood

Patent Assignee: MICROHEART INC (MICR-N); SCIMED LIFE SYSTEMS INC (SCIM-N)
Inventor: **CHEE U H** ; **MUELLER R L**
Number of Countries: 030 Number of Patents: 006
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200132088	A2	20010510	WO 2000US41905	A	20001103	200136	B
AU 200136424	A	20010514	AU 200136424	A	20001103	200149	
EP 1229845	A2	20020814	EP 2000991944	A	20001103	200261	
			WO 2000US41905	A	20001103		
US 6524324	B1	20030225	US 99163704	P	19991105	200323	
			US 2000706016	A	20001103		
JP 2003512884	W	20030408	WO 2000US41905	A	20001103	200333	
			JP 2001534300	A	20001103		
US 20030114872	A1	20030619	US 99163704	P	19991105	200341	
			US 2000706016	A	20001103		
			US 2002304025	A	20021125		

Priority Applications (No Type Date): US 99163704 P 19991105; US 2000706016 A 20001103; US 2002304025 A 20021125
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200132088	A2	E	43	A61B-017/34	
Designated States (National): AU CA JP					
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
AU 200136424	A			A61B-017/34	Based on patent WO 200132088
EP 1229845	A2	E		A61B-017/34	Based on patent WO 200132088
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 6524324	B1			A61B-017/34	Provisional application US 99163704
JP 2003512884	W		64	A61B-017/00	Based on patent WO 200132088
US 20030114872	A1			A61B-017/32	Provisional application US 99163704
					Div ex application US 2000706016
					Div ex patent US 6524324

STIC Search Report
EIC 3700

STIC Database Tracking Number: 108741

TO:	From:
Jeoyuh Lin **Location: cp2 4c08** **Art Unit: 3737** **Friday, November 28, 2003** **Case Serial Number: 09/706584**	**John Sims** **Location: EIC 3700** **CP2, 2C08** **Phone: 308-4836** **john.sims@uspto.gov**

Search Notes

Please examine your results carefully. This search employed a large number of search terms, so the results may or may not be on point.

Search and Information Resources Administration

14/3,KWIC/3 (Item 3 from file: 350)
DIALOG(R)File 350:Derwent WPIX

015051429
WPI Acc No: 2003-111945/200310
Related WPI Acc No: 1996-412586; 1998-610127; 1999-527341; 2001-316488
XRAM Acc No: C03-028637

Increasing contractile function in the heart of a patient, useful for treating heart diseases such as cardiovascular diseases, comprises delivering a transgene encoding an angiogenic protein or peptide to at least one coronary artery

Patent Assignee: DILLMANN W (DILL-I); GIORDANO F J (GIOR-I); HAMMOND H K (HAMM-I); UNIV CALIFORNIA (REGC)
Inventor: DILLMANN W; GIORDANO F J; HAMMOND H K
Number of Countries: 100 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200289856	A1	20021114	WO 2002US13990	A	20020503	200310 B
US 20030148968	A1	20030807	US 95396207	A	19950228	200358
			US 95485472	A	19950607	
			US 97852779	A	19970507	
			US 97722271	A	19971229	
			US 9821773	A	19980211	
			US 9868102	A	19980430	
			US 98132167	A	19980810	
			WO 99US2702	A	19990209	
			US 99435156	A	19991105	
			US 2000609080	A	20000630	
			WO 2000US30345	A	20001103	
			US 2001847936	A	20010503	

Priority Applications (No Type Date): US 2001847936 A 20010503; US 95396207 A 19950228; US 95485472 A 19950607; US 97852779 A 19970507; US 97722271 A 19971229; US 9821773 A 19980211; US 9868102 A 19980430; US 98132167 A 19980810; WO 99US2702 A 19990209; US 99435156 A 19991105; US 2000609080 A 20000630; WO 2000US30345 A 20001103
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200289856	A1	E	129	A61K-048/00	
	Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW				
	Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW				
US 20030148968	A1			A61K-048/00	CIP of application US 95396207
					CIP of application US 95485472
					Cont of application US 97852779
					CIP of application US 97722271
					CIP of application US 9821773
					CIP of application US 9868102
					Cont of application US 98132167
					CIP of application WO 99US2702
					CIP of application US 99435156
					CIP of application US 2000609080
					CIP of application WO 2000US30345
					CIP of patent US 5792453
					CIP of patent US 6100242
					Cont of patent US 6174871

Abstract (Basic):

... the power 11 viral particles of recombinant adenovirus was delivered by slow injection into both left and right coronary arteries. Two-dimensional and M-mode **images** were obtained from a right parasternal approach at the papillary muscle level. Studies were performed 1 day before gene transfer and repeated 14 days later...

...The method is useful for treating **heart** diseases including cardiovascular diseases, peripheral vascular diseases, congestive **heart** failure, dilated cardiomyopathy, dilated cardiomyopathy. The method is also useful for increasing blood flow in an **ischemic** tissue of a patient, for increasing contractile function on the **heart** of the patient, and for preventing or alleviating deleterious ventricular remodeling in a patient who has suffered a myocardial infarction...

Technology Focus:

... The vector may also be introduced by injection from a catheter conducted at least 1 cm into the lumen of the arteries, or by retrograde **perfusion** from a catheter placed into a conduit receiving blood from the myocardium. The vector is introduced into a saphenous vein graft and/or an internal...

...an insulin-like growth factor, a hypoxia-inducible factor and an angiogenic polypeptide regulator. The angiogenic protein or peptide stimulates collateral vessel development in the **heart** , thus enhancing blood flow in the **heart** . The vector further comprises a transgene encoding a **cardiac** enhancing protein or peptide, which is a beta-adrenergic signaling protein or peptide (beta-ASP), and which induces the growth or function of myocytes, thus enhancing contractile function in the **heart** . Delivery of the transgene using the vector is predominantly localized to the **heart** , where the vector predominantly transfects **cardiac** cells. Expression of the transgene occurs predominantly within the myocardium, particularly within **cardiac** myocytes. The percent wall thickening in the **heart** is increased. Introduction of the vector into at least one coronary artery may be performed coincident with or following infusion of the artery with a...

...1 ml/minute for about 3 minutes prior to the injection of the vector. The patient has a cardiovascular disease such as atherosclerosis or myocardial **ischemia** . Blood flow within the **heart** is increased. Increasing blood flow in an **ischemic** tissue of a patient comprises delivering a transgene encoding an angiogenic protein or peptide to an **ischemic** region of the tissue by introducing a vector comprising the transgene to the tissue, where the transgene is expressed in the tissue, and subsequently increase blood flow in the tissue. The patient has cardiovascular disease, particularly peripheral vascular disease. The vector is introduced into the tissue by anterograde **perfusion** from a catheter placed into a conduit delivering blood to the tissue, or by retrograde **perfusion** from a catheter placed into a conduit receiving blood from the tissue. The **ischemic** tissue comprises muscle cells, specifically **cardiac** myocytes, where increasing blood flow within the **ischemic** tissue results in increased contractile function. The conduit delivering blood to the tissue is a coronary artery or a femoral artery. The vector is introduced...

...injecting a solution comprising the vector into skeletal muscle, where the angiogenic protein or peptide causes an increase in blood flow and a decrease in **ischemia** in the tissue. The solution comprises at least about one ml. The angiogenic protein or peptide stimulates collateral vessel development in the **heart** , thus enhancing blood flow in the **heart** .

John Sims EIC 3700 308-4836

JLin

CORPORATE SOURCE: Angiogenic GENe Therapy (AGENT-2) Study Group, Department of Medicine, Section of Cardiology, William Beaumont Hospital, Royal Oak, MI, USA
SOURCE: Journal of the American College of Cardiology (2003), 42(8), 1339-1347
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objectives The primary objective of this study was to determine whether intracoronary administration of the adenoviral gene for fibroblast growth factor (Ad5FGF-4) can improve **myocardial perfusion** compared with placebo. Background Animal studies and observational clin. studies have shown improvement in **perfusion** of the **ischemic myocardium** using genes encoding angiogenic growth factors; however, randomized, double-blind data in humans are lacking. Methods We performed a randomized, double-blind, placebo-controlled trial of intracoronary injection of 1010 adenoviral particles containing a gene encoding fibroblast growth factor (Ad5FGF-4) to determine the effect on **myocardial perfusion**. Fifty-two patients with stable angina and reversible **ischemia** comprising >9% of the left ventricle on adenosine single-photon emission computed tomog. (**SPECT**) **imaging** were randomized to gene therapy (n = 35) or placebo (n = 17). Clin. follow-up was performed, and 51 (98%) patients underwent a second adenosine **SPECT** scan after 8 wk. Results Overall (n = 52), the mean total **perfusion** defect size at baseline was 32.4% of the left ventricle, with 20% reversible **ischemia** and 12.5% scar. At eight weeks, Ad5FGF-4 injection resulted in a significant reduction of **ischemic** defect size (4.2% absolute, 21% relative; $p < 0.001$) and placebo-treated patients had no improvement ($p = 0.32$). Although the change in reversible **perfusion** defect size between Ad5FGF-4 and placebo was not significant (4.2% vs. 1.6%, $p = 0.14$), when a single outlier was excluded a significant difference was observed (4.2% vs. 0.8%, $p < 0.05$). Ad5FGF-4 was well tolerated and did not result in any permanent adverse sequelae. Conclusions Intracoronary injection of Ad5FGF-4 showed an encouraging trend for improved **myocardial perfusion**; however, further studies of therapeutic **angiogenesis** with Ad5FGF-4 will be necessary.

L17 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:481702 HCAPLUS
DOCUMENT NUMBER: 137:197543
TITLE: Medical **imaging** techniques in the evaluation of strategies for therapeutic **angiogenesis**
AUTHOR(S): Pearlman, Justin D.; Laham, Roger J.; Post, Mark; Leiner, Tim; Simons, Michael
CORPORATE SOURCE: Departments of Medicine and Radiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, 03755, USA
SOURCE: Current Pharmaceutical Design (2002), 8(16), 1467-1496
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Recent advancements in our understanding of the basic biol. of **angiogenesis** have prompted a focus on practical applications, both in cardiovascular disease and in oncol. The focus on practical applications has stimulated development of novel noninvasive tools that

JLin

Stimulation vs
Nov b v. growth
No substance

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(2), 795-802
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Therapeutic **angiogenesis** is a novel approach to the treatment of **myocardial ischemia** based on the use of proangiogenic growth factors to induce the growth of new blood vessels to supply the **myocardium** at risk. This study was designed to assess the safety and efficacy of a single intrapericardial injection of basic fibroblast growth factor (FGF-2) in a porcine model of chronic **myocardial ischemia**. Yorkshire pigs underwent ameroid placement around the left circumflex coronary artery. At 3 wk, animals were randomized to receive a single intrapericardial injection of either saline (n = 10), 3 mg of heparin (n=9), 3 mg of heparin +30 μg of FGF-2 (n = 10), 200 μg of FGF-2 (n = 10), or 2 mg of FGF-2 (n = 10). Coronary angiog., microsphere flow, **magnetic resonance** functional, and **perfusion imaging** were performed before and 4 wk after treatment, at which time histol. anal. was also performed on 3 animals in each group. In **ischemic** pigs, FGF-2 treatment resulted in significant increases in left-to-left angiog. collaterals and left circumflex coronary artery blood flow. These benefits were accompanied by improvements in **myocardial perfusion** and function in the **ischemic** territory, as well as histol. evidence of increased **myocardial** vascularity without any adverse effects. Not one of these benefits was seen in saline- or heparin-treated **ischemic** animals. A single intrapericardial injection of FGF-2 in a porcine model of chronic **myocardial ischemia** results in functionally significant **myocardial angiogenesis**, without any adverse outcomes. This mode of FGF-2 administration may prove to be a useful therapeutic strategy for the treatment of patients with **ischemic heart** disease.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:750406 HCAPLUS
DOCUMENT NUMBER: 131:347070
TITLE: Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial
AUTHOR(S): Laham, Roger J.; Sellke, Frank W.; Edelman, Elazer R.; Pearlman, Justin D.; Ware, J. Anthony; Brown, David L.; Gold, Jeffrey P.; Simons, Michael
CORPORATE SOURCE: Angiogenesis Research Center, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA
SOURCE: Circulation (1999), 100(18), 1865-1871
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiogenesis** is a promising treatment strategy for patients who are not candidates for standard revascularization, because it promotes the growth of new blood vessels in **ischemic myocardium**. We conducted a randomized, double-blind, placebo controlled study of basic

the moment of injection. Serial ECGs showed no evidence of new **myocardial** infarction in any patient. Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110 to 395 cm3. Postoperative **cardiac** output fell transiently but increased within 24 h (preanesthesia=4.8 vs. postanesthesia=4.1 vs. 24 h postoperative=6.3). Time to extubation after closure was 18.4 min; average postoperative hospital stay was 3.8 days. All patients had significant reduction in angina (nitroglycerin [NTG] use=53.9/wk pre-GTx vs. 9.8/wk post-GTx). Postoperative left ventricular ejection fraction (LVEF) was either unchanged or improved (mean increase in LVEF=5%). Objective evidence of reduced **ischemia** was documented using dobutamine single photon emission computed tomog. (**SPECT**)-sestamibi **imaging** in all patients. Coronary angiog. showed improved Rentrop score in 5 of 5 patients. This initial experience with naked gene transfer as sole therapy for **myocardial ischemia** suggests that direct **myocardial** injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved **myocardial perfusion** in selected patients with chronic **myocardial ischemia**.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:93637 HCAPLUS

DOCUMENT NUMBER: 128:213011

TITLE: Biologic bypass with the use of adenovirus-mediated gene transfer of the complementary deoxyribonucleic acid for vascular endothelial growth factor 121 improves **myocardial perfusion** and function in the **ischemic** porcine **heart**

growth factor improves function in ischemic heart

AUTHOR(S): Mack, Charles A.; Patel, Shailen R.; Schwarz, Eric A.; Zanzonico, Pat; Hahn, Rebecca T.; Ilercil, Arzu; Devereux, Richard B.; Goldsmith, Stanley J.; Christian, Timothy F.; Sanborn, Timothy A.; Kovesdi, Imre; Hackett, Neil; Isom, O. Wayne; Crystal, Ronald G.; Rosengart, Todd K.

CORPORATE SOURCE: Department of Cardiothoracic Surgery, The New York Hospital-Cornell Medical Center, New York, NY, 10021, USA

SOURCE: Journal of Thoracic and Cardiovascular Surgery (1998), 115(1), 168-177
CODEN: JTCSAQ; ISSN: 0022-5223

PUBLISHER: Mosby-Year Book, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vascular endothelial growth factor (VEGF), a potent angiogenic mediator, can be delivered to targeted tissues by means of a replication-deficient adenovirus (Ad) vector. We hypothesized that direct administration of Ad vector expressing the VEGF121 complementary DNA (AdGVVEGF121.10) into regions of **ischemic myocardium** would enhance collateral vessel formation and improve regional **perfusion** and function. Yorkshire swine underwent thoracotomy and placement of an Ameroid constrictor (Research Instruments & MFG, Corvallis, Ore.) on the circumflex coronary artery. Three weeks later, **myocardial perfusion** and function were assessed by single photon emission computed tomog. **imaging** (**SPECT**) with 99mTc-labeled sestamibi and by echocardiog. during rest and stress. AdGVVEGF121.10 (n = 7) or the control vector, AdNull (n = 8), was administered directly into

20/3,KWIC/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07200537 Genuine Article#: 135PB No. References: 31
Title: VEGF administration in chronic myocardial ischemia **in pigs**
Author(s): Lopez JJ; Laham RJ; Stamler A; Pearlman JD; Bunting S; Kaplan A; Carrozza JP; Sellke FW; Simons M (REPRINT)
Corporate Source: BETH ISRAEL DEACONESS MED CTR,ANGIOGENESIS RES CTR/BOSTON//MA/02215 (REPRINT); BETH ISRAEL DEACONESS MED CTR,ANGIOGENESIS RES CTR/BOSTON//MA/02215; HARVARD UNIV,SCH MED/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR,DIV CARDIOVASC/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR,DEPT SURG/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR,DEPT RADIOL/BOSTON//MA/ ; LOCAL MED,/PALO ALTO//CA/; GENENTECH INC,/S SAN FRANCISCO//CA/94080
Journal: CARDIOVASCULAR RESEARCH, **1998** , V40, N2 (NOV), P272-281
ISSN: 0008-6363 Publication date: 19981100
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: VEGF administration in chronic myocardial ischemia **in pigs , 1998**
Abstract: Objective: Previous investigations have shown the effectiveness of sustained intra- or extravascular administration of vascular endothelial growth factor (VEGF) in chronic **myocardial ischemia** in improvement of left ventricular function. The present investigations were undertaken in order to evaluate efficacy of a single bolus or local intracoronary delivery. Methods...

...received intracoronary administration of saline and served as a control (n = 9). Three weeks after initiation of therapy, the animals were evaluated with regard to **myocardial** perfusion and global as well as regional ventricular function. Results: All three VEGF treatment groups but not the control animals demonstrated a significant increase in the left-to-left (but not right-to-left) collateral index, **myocardial** blood flow (pre-therapy LCX vs. LAD (average of all groups): 0.76 +/- 0.35 vs. 0.96 +/- 0.38 ml*min(-1)*g(-1...

...control animals (21 +/- 3.3 vs. 27 +/- 5.8, p = NS). Conclusion: Single intracoronary delivery (intravascular bolus or local delivery) of VEGF is effective in **stimulating** physiologically significant **angiogenesis** in porcine model of chronic **myocardial ischemia** . (C) 1998 Elsevier Science B.V. All rights reserved.
...Identifiers--FIBROBLAST GROWTH-FACTOR; CORONARY COLLATERAL DEVELOPMENT; ARTERY OCCLUSION; BLOOD-FLOW; THERAPEUTIC **ANGIOGENESIS** ; PORCINE **HEARTS** ; LIMB **ISCHEMIA** ; RABBIT MODEL; DISEASE

20/3,KWIC/3 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06691412 Genuine Article#: ZK771 No. References: 66
Title: Arterial gene transfer of naked DNA for therapeutic angiogenesis : **early clinical results**
Author(s): Isner JM (REPRINT)
Corporate Source: TUFTS UNIV,SCH MED, DEPT MED/BOSTON//MA/02135 (REPRINT); TUFTS UNIV,SCH MED, DEPT BIOMED RES/BOSTON//MA/02135; TUFTS UNIV,SCH MED, DEPT RADIOL/BOSTON//MA/02135; TUFTS UNIV,SCH MED, ST ELIZABETHS MED CTR, DEPT SURG/BOSTON//MA/02135

John Sims EIC 3700 308-4836

11/3,KWIC/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013121573 BIOSIS NO.: 200100293412
Alleviation of myocardial ischemia after Kawasaki disease by heparin and exercise therapy
AUTHOR: Tateno Shigeru; Terai Masaru (Reprint); Niwa Koichiro; Jibiki Toshiaki; Hamada Hiromichi; Yasukawa Kumi; Honda Takafumi; Oana Shinji; Kohno Yoichi
AUTHOR ADDRESS: Department of Pediatrics, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba, 260-8670, Japan** Japan
JOURNAL: Circulation 103 (21): p2591-2597 May 29, 2001 2001
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Heparin **promotes angiogenesis** . We evaluated the effects of combined treatment with heparin and **exercise** on myocardial ischemia in the chronic stage of Kawasaki disease. Methods and Results: This study was conducted in 7 patients (aged 6 to 19 years) who had a totally occluded coronary artery and stress-induced myocardial ischemia in the collateral-dependent areas. Twice-daily **exercise** using a bicycle ergometer was performed with increments of 0.5 W/kg every 3 minutes up to maximal exertion for 10 days. Heparin, which immediately increased circulating hepatocyte growth factor, was given intravenously 10 minutes before each **exercise** period. Newly developed myocardial infarction, ventricular tachyarrhythmia, anginal attack, or hemorrhagic complication was not observed in any patient. Dipyridamole-loading single photon emission computed tomography documented improved myocardial **perfusion** in the collateral-dependent areas and a significant reduction in total defect scores in all patients after the completion of 20 sessions (P=0.01). In control patients who did not receive the heparin- **exercise** therapy, however, stress defect scores remained unchanged (n=1) or increased (n=2) during follow-up. Computerized quantitative coronary angiography provided evidence that the heparin- **exercise** therapy increased the diameter of the occluded artery to which collaterals terminated (P=0.001) but not that of the reference artery with which collaterals were not connected (P=0.96). Conclusions: The findings suggest that a series of heparin and **exercise** treatments over 10 days may have a dramatic effect on the alleviation of myocardial ischemia in collateral-dependent regions. This may be a safe, noninvasive...
? t s11/3,kwic/2-10

Hep + Exercise Bridge to Stilbin?

11/3,KWIC/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011650242 BIOSIS NO.: 199800444489
Exercise training in swine promotes **growth of arteriolar bed and capillary** angiogenesis **in heart**
AUTHOR: White Francis C; Bloor Colin M; McKirnan M Dan; Carroll Susan M (Reprint)
AUTHOR ADDRESS: Univ. Calfironia San Diego Sch. Med., 9500 Gilman Dr., La Jolla, CA 92093-0612, USA**USA
JOURNAL: Journal of Applied Physiology 85 (3): p1160-1168 Sept., 1998 1998
MEDIUM: print

ISSN: 8750-7587
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Exercise training in swine promotes **growth of arteriolar bed and capillary** angiogenesis **in heart**

ABSTRACT: **Exercise** training induces coronary vascular adaptations. The goal of this study was to contrast the effects of training on capillary and arteriolar growth. Minipigs were trained...
...Maximal O2 consumption increased continuously throughout the study. Capillary and arteriolar densities and diameters, and proliferation of vascular cells in these vessels, were determined in **perfusion** -fixed tissue. The arterioles were subdivided into five groups according to diameter: 10-19.9, 20-30, 31-40, 41-70, and 71-120 mum...
DESCRIPTORS:
MISCELLANEOUS TERMS: capillary **angiogenesis** ;

11/3,KWIC/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010817341 BIOSIS NO.: 199799451401
Basic fibroblast growth factor as a biochemical marker of exercise-induced ischemia
AUTHOR: Gu Jian-Wei; Santiago Derek; Olowe Yetunde; Weinberger Judah (Reprint)
AUTHOR ADDRESS: Columbia-Presbyterian Hosp., 161 Fort Washington Ave., New York, NY 10032, USA**USA
JOURNAL: Circulation 95 (5): p1165-1168 1997 1997
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

...ABSTRACT: with metastatic tumors, but its expression in human myocardial ischemia is unknown. Thus, we sought to determine whether urine levels of bFGF are altered by **exercise** -induced ischemia in humans. Methods and Results. Eighty-six patients underwent **exercise** thallium studies for evaluation of anginal symptoms. Urine levels of bFGF (corrected for urine creatinine) were determined by ELISA immediately before and between 2 and 4 hours after **exercise** . The change in urine bFGF level was compared between 43 patients with and 43 patients without **exercise** -induced ischemia. Patients with ischemia had an increase in urine bFGF compared with nonischemic patients (1052+-245 versus -278+-130 pg/g creatinine, P lt .0001). **Exercise** , demographic, and clinical variables were assessed and analyzed for possible effect on bFGF response to **exercise** . By univariate analysis, a history of hypertension was negatively associated with a change in bFGF level (P lt .05). No other variables were associated. By multivariate analysis, only bFGF response (P lt .001) and age (P lt .05) were independently related to **exercise** -induced ischemia. Conclusions. Significantly increased levels of bFGF are detected in the urine within hours of **exercise** -induced ischemia. Further studies are warranted to determine whether bFGF might serve as a useful circulating marker of myocardial ischemia in humans.

11/3,KWIC/4 (Item 4 from file: 5)

Title: EFFECT OF CORONARY COLLATERAL CIRCULATION ON MYOCARDIAL-ISCHEMIA AND VENTRICULAR DYSFUNCTION
Author(s): SASAYAMA S
Corporate Source: KYOTO UNIV,DEPT INTERNAL MED,DIV 3,SAKYO KU,54 KAWARACHO,SHOGOIN/KYOTO 606//JAPAN/
Journal: CARDIOVASCULAR DRUGS AND THERAPY, 1994, V8, S2 (MAY), P327-334
ISSN: 0920-3206
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: observed the following facts in our studies during intracoronary thrombolytic therapy: (a) Myocardial ischemia is important for the development of collateral circulation, (b) collaterals can **perfuse** the infarcted myocardium, and (c) the presence of collaterals prevents the left ventricular aneurysm formation in acute myocardial infarction, even when the amount of the ...

...merely markers of severe ischemia but help to preserve the functional integrity of the myocardium in the presence of coronary obstruction. We then attempted to **promote** collateralization to treat patients with angina pectoris. Patients with chronic stable effort angina were treated with heparin followed by treadmill **exercise** twice a day for 10 days. Treadmill capacity was found to improve in association with an increase in coronary collateral circulation. Heparin treatment of ischemic...
...Identifiers--TREADMILL CAPACITY; ANEURYSM FORMATION; ARTERY OCCLUSION; EFFORT ANGINA; INFARCTION; HEPARIN; FLOW; **ANGIOGENESIS;** ANASTOMOSES; REPERFUSION

Exercise
Help

11/3,KWIC/7 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03337293 Genuine Article#: NW496 No. References: 49
Title: BIPHASIC INDUCTION OF IMMEDIATE-EARLY GENE-EXPRESSION ACCOMPANIES ACTIVITY-DEPENDENT ANGIOGENESIS **AND MYOFIBER REMODELING OF RABBIT SKELETAL-MUSCLE**
Author(s): MICHEL JB; ORDWAY GA; RICHARDSON JA; WILLIAMS RS
Corporate Source: UNIV TEXAS,SW MED CTR,RYBURN CTR MOLEC CARDIOL,DEPT INTERNAL MED,NB 11200,5323 HARRY HINES BLVD/DALLAS//TX/75235; UNIV TEXAS,SW MED CTR,RYBURN CTR MOLEC CARDIOL,DEPT INTERNAL MED/DALLAS//TX/75235; UNIV TEXAS,SW MED CTR,DEPT BIOCHEM/DALLAS//TX/75235; UNIV TEXAS,SW MED CTR,DEPT PHYSIOL/DALLAS//TX/75235; UNIV TEXAS,SW MED CTR,DEPT PATHOL/DALLAS//TX/75235
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1994, V94, N1 (JUL), P277-285
ISSN: 0021-9738
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: BIPHASIC INDUCTION OF IMMEDIATE-EARLY GENE-EXPRESSION ACCOMPANIES ACTIVITY-DEPENDENT ANGIOGENESIS **AND MYOFIBER REMODELING OF RABBIT0 SKELETAL-MUSCLE**
Abstract: Sustained contractile activity of skeletal muscle **promotes angiogenesis** , as well as transformation of contractile protein isoforms and mitochondrial proliferation within myofibers. Since the products of immediate early genes such as c-fos, c...
...Research Fronts: 002 (C-FOS INDUCTION; EXPRESSION OF GENES ENCODING TRANSCRIPTION FACTORS; RAT SUPRACHIASMATIC NUCLEUS CELLS; CORTICAL STIMULATION; STRIATAL NEURONS)

John Sims EIC 3700 308-4836

Angiogenic gene therapy for stable angina is aimed at **promoting** new blood vessel formation in the heart, thus providing enhanced cardiac **perfusion** , symptom relief, increased **exercise** capacity, improved quality of life, and reduced risk of coronary events. Ad5FGF-4 is a replication-deficient serotype 5 adenovirus encoding the gene for fibroblast growth factor-4 (FGF-4) driven by a cytomegalovirus **promoter** . In preclinical studies using a pig model of myocardial ischemia, a single intracoronary infusion of Ad5FGF-4 improved cardiac contractile function and regional blood flow in the ischemic region during stress. These effects were apparent after 2 weeks and maintained for > or =12 weeks. Histologic evidence of capillary **angiogenesis** was observed. FGF-4 gene expression was detected in the heart but not at extracardiac sites. Placebo-controlled trials in humans with chronic stable angina indicate that Ad5FGF-4 increases treadmill **exercise** duration and improves stress-related ischemia measured by **perfusion** sestamibi single-photon emission computed tomography. More patients receiving Ad5FGF-4 than placebo reported complete resolution of their angina and no nitroglycerin use. Ad5FGF-4...
?

Growth Factors promoting perfusion, exercise not part of treatment

John Sims EIC 3700 308-4836

provide serial assessment of ongoing vessel growth in vivo. Nuclear **imaging** (**SPECT**, **PET**) and x-ray angiog. have been used to assess changes in **perfusion** and anat. appearance, resp., after induced neovascular development. New **MRI** techniques provide the ability to identify early changes in vivo that are more sensitive to detection of the effects of new vessel growth than x-ray angiog. or nuclear **imaging**. These new **MRI** techniques include measurement of blood delivery to the **myocardium**, development of intramyocardial vasculature, and incremental changes in regional **myocardial** contractile function. With the combination of methods now available, we expect to be able to track key steps of **angiogenesis** in vivo and to assess the efficacy of angiogenic therapies. These new **imaging** capabilities offer crucial information which we hope will hasten the identification and deployment of effective pharmaceutical therapies as an adjunct or alternative to invasive treatments of **ischemic** disease by targeted stimulation of **angiogenesis**, and of cancer, by targeted inhibition of **angiogenesis**.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:894999 HCAPLUS
DOCUMENT NUMBER: 137:72895
TITLE: Effects of intramyocardial injection of phVEGF-A165 as sole therapy in patients with refractory coronary artery disease - 12-month follow-up: Angiogenic gene therapy
AUTHOR(S): Sarkar, N.; Ruck, A.; Kallner, G.; Y-Hassan, S.; Blomberg, P.; Islam, K. B.; Van Der Linden, J.; Lindblom, D.; Nygren, A. T.; Lind, B.; Brodin, L.-A.; Drvota, V.; Sylven, C.
CORPORATE SOURCE: Departments of Cardiology, Huddinge University Hospital, Stockholm, Swed.
SOURCE: Journal of Internal Medicine (2001), 250(5), 373-381
CODEN: JINMEO; ISSN: 0954-6820
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective. The objective was to test the safety and bioactivity of phVEGF-A165 after intramyocardial injection during 12-mo follow-up. Inclusion criteria were angina pectoris, Canadian Cardiovascular Society (CCS) class III-IV, unamenable to further revascularization, ejection fraction (EF) >30%, **perfusion** defects extending over >10% of the anterolateral left ventricle wall detectable with adenosine single photon emission computerized tomog. (**SPECT**) and at least one patent vessel visible by coronary angiog. Seven of 39 patients referred for gene therapy were included. Via a mini-thoracotomy under general anesthesia, phVEGF-A165 was injected directly into the **myocardium** at four sites in the anterolateral region of the left ventricle. Operative procedures were uneventful. Perioperative release of **myocardial** markers and ECG changes were detected in two patients. There were no perioperative deaths but one patient died 7 mo postoperatively because of **myocardial** infarction. Plasma vascular endothelial growth factor (VEGF)-A levels increased two to threefold peaking 6 days postoperatively ($P < 0.004$) and returning to baseline by day 30. A significant reduction in angina pectoris was reported. The CCS class improved from 3.3 ± 0.2 to 1.9 ± 0.3 ($P < 0.01$) and nitroglycerin intake decreased from 39 ± 15 to 12 ± 5 tablets week-1 ($P < 0.001$) 2 mo after gene transfer. Improvements

remained after 12 mo when nitroglycerin consumption approached zero. Improved **myocardial** function in the phVEGF-A165 injection region was documented in all patients ($P < 0.016$) by tissue velocity **imaging** (TVI). Reduced reversible **ischemia** was detected by adenosine **SPECT** in four patients. Improved collateralization was detected in four patients with coronary angiog. Conclusion. Intramyocardial injection of phVEGF-A165 is safe and may lead to improved **myocardial perfusion** and function with longstanding symptomatic relief in end-stage angina pectoris. Based on these results this therapeutic potential is being tested in a double-blind placebo controlled multicenter trial.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:644118 HCAPLUS
DOCUMENT NUMBER: 136:64564
TITLE: Therapeutic **angiogenesis** with the use of vascular endothelial growth factor 165 gene in the **myocardium** of miniature swine
AUTHOR(S): Zhang, Duanzhen; Gai, Luyue; Chen, Yiwang; Fan, Ruiyun; Wen, Yingfeng; Dong, Wei
CORPORATE SOURCE: Department of Cardiology, the Chinese PLA General Hospital, Beijing, 100853, Peop. Rep. China
SOURCE: Shengli Xuebao (2001), 53(3), 183-187
CODEN: SLHPAH; ISSN: 0371-0874
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Effects of adenovirus-mediated VEGF 165 (VEGF165) on collateral vessel formation of coronary artery and improve regional **myocardial perfusion** and function were studied in a miniature swine model of chronic **myocardial ischemia**. Th recombinant adenovirus vector containing complementary DNA (cDNA) for human VEGF165 (Ad-VEGF165) or for β-galactosidase (Ad -Gal) was administered directly into the **ischemic myocardium** in the left circumflex (LCX) distribution. **Myocardial perfusion** and function were assessed by ECG -gated single photon emission computed tomog. **imaging** and collateral vessel development of coronary artery was assessed by ex vivo coronary angiog. (CAG). 4 Wk after Ad-VEGF165 administration, **SPECT imaging** demonstrated a significant reduction in **ischemic** area and **ischemic** severity, and a substantial improvement in left ventricular ejection fraction and regional wall motion in the LCX distribution, as compared with those of control animals and those before administration of Ad-VEGF165. Collateral vessel development with Rentrop Grading was also significantly greater in Ad-VEGF165 animals than that in the Ad-Gal control animals. It shows that Ad-VEGF165 can induce collateral vessel development in **ischemic myocardium** and result in significant improvement in **myocardial perfusion** and function.

L17 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:475502 HCAPLUS
DOCUMENT NUMBER: 133:94539
TITLE: Composition and formulations and their use as nociceptic, anti-anxiolytic and anabolic agents
INVENTOR(S): Nyce, Jonathan W.
PATENT ASSIGNEE(S): USA

JLin

SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040172	A1	20000713	WO 2000-US180	20000105
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356368	AA	20000713	CA 2000-2356368	20000105
EP 1139913	A1	20011010	EP 2000-904212	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 2000007397	A	20011030	BR 2000-7397	20000105
JP 2003523933	T2	20030812	JP 2000-591931	20000105
US 2003202935	A1	20031030	US 2000-554485	20000509

PRIORITY APPLN. INFO.: US 1999-114773P P 19990105
WO 2000-US180 W 20000105

AB Composition and formulations comprising a first agent such as folinic acid, pharmaceutically acceptable salts thereof or mixts. thereof, and a second agent(s) such as analgesics, muscle relaxants, mood disorder agents, anti-inflammatories, anti-migraine agents, anti-emetics, diuretics, high protein composites, and the like are claimed. The products are suitable as nociceptics and for the treatment of wasting disorders, bulimia, anorexia nervosa, anxiety, irritability and other symptoms associated with premenstrual syndrome, as well as for administration either in conjunction with steroids or to compensate adenosine depletion and/or bizarre behavior or aggression common in steroid users. Administration of dehydroepiandrosterone (300 mg/kg) or methyltestosterone (40 mg/kg) daily to rats for 2 wk showed multi-organ depletion of adenosine. Co-administration of folinic acid completely abrogated adenosine depletion. Folinic acid administered alone induced increase in adenosine levels for all organs studied.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:81371 HCAPLUS
DOCUMENT NUMBER: 132:203377
TITLE: Intrapericardial delivery of fibroblast growth factor-2 induces neovascularization in a porcine model of chronic **myocardial ischemia**
AUTHOR(S): Laham, Roger J.; Rezaee, Mehrdad; Post, Mark; Novicki, Debborah; Sellke, Frank W.; Pearlman, Justin D.; Simons, Michael; Hung, David
CORPORATE SOURCE: Angiogenesis Research Center and Interventional Cardiology Section, Department of Medicine, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA

JLin

L17 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:175034 HCAPLUS
DOCUMENT NUMBER: 139:63736
TITLE: The VIVA trial: vascular endothelial **growth factor** in **ischemia** for vascular **angiogenesis**
AUTHOR(S): Henry, Timothy D.; Annex, Brian H.; McKendall, George R.; Azrin, Michael A.; Lopez, John J.; Giordano, Frank J.; Shah, P. K.; Willerson, James T.; Benza, Raymond L.; Berman, Daniel S.; Gibson, C. Michael; Bajamonde, Alex; Rundle, Amy Chen; Fine, Jennifer; McCluskey, Edward R.
CORPORATE SOURCE: Div. Cardiol. at Hennepin County Med. Cent., University of Minnesota, Minneapolis, MN, 55407, USA
SOURCE: Circulation (2003), 107(10), 1359-1365
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recombinant human vascular endothelial **growth factor** protein (rhVEGF) **stimulates angiogenesis** in animal models and was well tolerated in Phase I clin. trials. VIVA (Vascular endothelial **growth factor** in **Ischemia** for Vascular **Angiogenesis**) is a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of intracoronary and i.v. infusions of rhVEGF. A total of 178 patients with stable exertional angina, unsuitable for standard revascularization, were randomized to receive placebo, low-dose rhVEGF (17 ng · kg-1 · min-1), or high-dose rhVEGF (50 ng · kg-1 · min-1) by intracoronary infusion on day 0, followed by i.v. infusions on days 3, 6, and exercise treadmill tests, angina class, and quality of life assessments were performed at baseline, day 60, and day 120. **Myocardial** perfusion **imaging** was performed at baseline and day 60. At day 60, the change in exercise treadmill test (ETT) time from baseline was not different between groups (placebo, +48 s; low dose, +30 s; high dose, +30 s). Angina class and quality of life were significantly improved within each group, with no difference between groups. By day 120, placebo-treated patients demonstrated reduced benefit in all three measures, with no significant difference compared with low-dose rhVEGF. In contrast, high-dose rhVEGF resulted in significant improvement in angina class (P=0.05) and nonsignificant trends in ETT time (P=0.15) and angina frequency (P=0.09) as compared with placebo. RhVEGF seems to be safe and well tolerated. RhVEGF offered no improvement beyond placebo in all measurements by day 60. By day 120, high-dose rhVEGF resulted in significant improvement in angina and favorable trends in ETT time and angina frequency.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:895952 HCAPLUS
TITLE: A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on **myocardial perfusion** in patients with stable angina
AUTHOR(S): Grines, Cindy L.; Watkins, Matthew W.; Mahmarian, John J.; Iskandrian, Ami E.; Rade, Jeffrey J.; Marrott, Pran; Pratt, Craig; Kleiman, Neal

...Title Terms: **ANGIOGENESIS** ;

John Sims EIC 3700 308-4836

severity of the **perfusion** abnormalities was calculated by two blinded investigators. Compared to baseline, there was no significant change in exercise duration or peak rate-pressure product achieved with either placebo or adenosine plus heparin. In comparison there was a significant reduction in the severity of myocardial **perfusion** abnormalities in patients who received adenosine plus heparin. The results showed that repeated administrations of adenosine and heparin reduced the exercise-induced **ischemia** in patients with chronic stable angina refractory to conventional treatment. Administration is continuous for 6 minutes/day for a week or more (claimed). Hepa

14/3,KWIC/5 (Item 5 from file: 350)
DIALOG(R)File 350:Derwent WPIX

012471095
WPI Acc No: 1999-277203/199923
XRAM Acc No: C99-081396

Treatment of occlusive peripheral vascular disease, coronary disease and associated disorders - comprises co-administration of adenosine A - 2 receptor agonist, e.g. adenosine, and heparin and/or a heparin-like substance in low, daily dosages for one week or more

Patent Assignee: UNIV CALIFORNIA (REGC)
Inventor: BARRON H V; BOTVINICK E
Number of Countries: 084 Number of Patents: 006
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9917784	A1	19990415	WO 98US21153	A	19981007	199923	B
AU 9897909	A	19990427	AU 9897909	A	19981007	199936	
US 5972903	A	19991026	US 97946196	A	19971007	199952	
EP 1021195	A1	20000726	EP 98952141	A	19981007	200037	
			WO 98US21153	A	19981007		
US 6440947	B1	20020827	US 97946196	A	19971007	200259	
			US 98167816	A	19981007		
JP 2003506310	W	20030218	WO 98US21153	A	19981007	200315	
			JP 2000514655	A	19981007		

Priority Applications (No Type Date): US 98167816 A 19981007; US 97946196 A 19971007
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9917784	A1	E	46	A61K-031/715	
Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
AU 9897909	A			A61K-031/715	Based on patent WO 9917784
US 5972903	A			A61K-031/70	
EP 1021195	A1	E		A61K-031/715	Based on patent WO 9917784
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6440947	B1			A61K-031/70	CIP of application US 97946196
JP 2003506310	W		46	A61K-031/727	Based on patent WO 9917784

...Abstract (Basic): and heparin and/or a heparin-like substance is used to treat occlusive peripheral vascular disease, coronary disease and associated disorders and to promote coronary **angiogenesis** (claimed). The treatment is used to improve collateral coronary circulation in patients suffering from myocardial infarction to restore **cardiac** function after myocardial infarction and to improve blood flow in patients with coronary artery disease suffering from myocardial **ischemia** or inadequate blood flow to areas other than the **heart** , e.g. occlusive peripheral vascular disease, where decreased blood flow is a problem. Subjects with chronic, stable angina refractory to conventional medical therapy and unsuited...

...bolus; n=9) or placebo (n=6), daily for 10 days. All patients underwent baseline and follow-up exercise testing with Thallium 201 SPECT myocardial **perfusion imaging** . A semi-quantitative assessment of the

fibroblast growth factor (bFGF; 10 or 100μg vs. placebo) delivered via sustained-release heparin-alginate microcapsules implanted in **ischemic** and viable but ungraftable **myocardial** territories in patients undergoing CABG. Twenty-four patients were randomized to 10 μg of bFGF (n=8), 100 μg of bFGF (n=8), or placebo (n=8), in addition to undergoing CABG. There were 2 operative deaths and 3 Q-wave **myocardial** infarctions. There were no treatment-related adverse events, and there was no rise in serum bFGF levels. Clin. follow-up was available for all patients (16.0±6.8 mo). Three control patients had recurrent angina, 2 of whom required repeat revascularization. One patient in the 10-μg bFGF group had angina, whereas all patients in the 100-μg bFGF group remained angina-free. Stress nuclear **perfusion imaging** at baseline and 3 mo after CABG showed a trend toward worsening of the defect size in the placebo group (20.7±3.7% to 23.8±5.7%, P=0.06), no significant change in the 10-μg bFGF group, and significant improvement in the 100-μg bFGF group (19.2±5.0% to 9.1±5.9%, P=0.01). **Magnetic resonance** assessment of the target **ischemic** zone in a subset of patients showed a trend toward a reduction in the target **ischemic** area in the 100-μg bFGF group (10.7±3.9% to 3.7±6.3%, P=0.06). This study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable **myocardium** that cannot be adequately revascularized.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:36422 HCAPLUS
DOCUMENT NUMBER: 130:261729
TITLE: Gene therapy for **myocardial** **angiogenesis** initial clinical results with direct **myocardial** injection of phVEGF165 as sole therapy for **myocardial** **ischemia**
AUTHOR(S): Losordo, Douglas W.; Vale, Peter R.; Symes, James F.; Dunnington, Cheryl H.; Esakof, Darryl D.; Maysky, Michael; Ashare, Alan B.; Lathi, Kishor; Isner, Jeffrey M.
CORPORATE SOURCE: Departments of Medicine, Biomedical Research, Surgery, and Anesthesiology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, 02135, USA
SOURCE: Circulation (1998), 98(25), 2800-2804
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors initiated a phase 1 clin. study to determine the safety and bioactivity of direct **myocardial** gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic **myocardial** **ischemia**. VEGF gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiog. documented coronary artery disease). Naked plasmid DNA encoding VEGF (phVEGF165) was injected directly into the **ischemic** **myocardium** via a mini left anterior thoracotomy. Injections caused no changes in **heart** rate (pre-GTx=75/min vs. post-GTx=80/min, P=NS), systolic BP (114 vs. 118 mm Hg, P=NS), or diastolic BP (57 vs. 59 mm Hg, P=NS). Ventricular arrhythmias were limited to single unifocal premature beats at

the **myocardium** at 10 sites in the circumflex distribution (108 pfu/site). Four weeks later, these studies were repeated and ex vivo angiog. was performed. **SPECT imaging** 4 wk after vector administration demonstrated significant reduction in the **ischemic** area at stress in AdGVVEFG121.10-treated animals compared with AdNull control animals ($p = 0.005$). Stress echocardiog. at the same time demonstrated improved segmental wall thickening in AdGVVEGF121.10 animals compared with AdNull control animals ($p = 0.03$), with AdGVVEGF121.10 animals showing nearly normalized function in the circumflex distribution. Collateral vessel development assessed by angiog. was also significantly greater in AdGVVEGF121.10 animals than in AdNull control animals ($p = 0.04$), with almost complete reconstitution of circumflex filling in AdGVVEGF121.10 animals. An Ad vector expressing the VEGF121 cDNA induces collateral vessel development in **ischemic myocardium** and results in significant improvement in both **myocardial perfusion** and function. Such a strategy may be useful in patients with **ischemic heart** disease in whom complete revascularization is not possible.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:845403 HCAPLUS

DOCUMENT NUMBER: 123:247600

TITLE: **Magnetic resonance** mapping demonstrates benefits of VEGF-induced **myocardial angiogenesis**

AUTHOR(S): Pearlman, Justin D.; Hibberd, Mark G.; Chuang, Michael L.; Harada, Kazumasa; Lopez, John J.; Gladstone, Stephen R.; Friedman, Menahem; Sellke, Frank W.; Simons, Michael

CORPORATE SOURCE: Department of Radiology, Harvard Medical School, Boston, MA, 02215, USA

SOURCE: Nature Medicine (New York) (1995), 1(10), 1085-9
CODEN: NAMEFI; ISSN: 1078-8956

PUBLISHER: Nature Publishing Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Coronary occlusive disease is the leading cause of death in industrial nations and affects one in 4 adults. Although **heart** attacks are caused by occlusion of a coronary artery, some patients have occlusions without infarction because they have sufficient collateral vessels providing an alternate pathway for blood supply. Vascular endothelial **growth factor** (VEGF) is an angiogenic peptide that can **stimulate** collateral vessel development in the **ischemic myocardium**. We used **magnetic resonance imaging** (**MRI**) and image processing to identify and quantify noninvasively the benefits related to VEGF infusion on collateral development in the **heart**. This was accomplished as a placebo-controlled study in the porcine model of chronic **ischemia** that most closely mimics the human pathophysiol. of progressive coronary occlusion. Image series converted to a space-time map demonstrated that with treatment the **ischemic** zone was smaller and the contrast arrival delay was less, which resulted in better ejection fraction and regional wall thickening. These findings demonstrate in a manner applicable to humans, that VEGF improves collateral blood supply, resulting in improved **cardiac** global and regional function after and in spite of coronary artery occlusion.

20/3,KWIC/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011635360 BIOSIS NO.: 199800429607
Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis **in the setting of tissue ischemia**
AUTHOR: Witzenbichler Bernhard; Asahara Takayuki; Murohara Toyoaki; Silver Marcy; Spyridoupoulos Ioakim; Magner Meredith; Principe Nicole; Kearney Marianne; Hu Jing-Shan; Isner Jeffrey M (Reprint)
AUTHOR ADDRESS: St. Elizabeth's Med. Cent. Boston, 736 Cambridge St., Boston, MA 02135, USA**USA
JOURNAL: American Journal of Pathology 153 (2): p381-394 Aug., 1998 **1998**
MEDIUM: print
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis **in the setting of tissue ischemia**
1998

...ABSTRACT: to development of the lymphatic vasculature. The current studies were designed to test the hypothesis that constitutive expression of VEGF-C in adult animals promotes **angiogenesis** . In vitro, VEGF-C exhibited a dose-dependent mitogenic and chemotactic effect on endothelial cells, particularly for microvascular endothelial cells (72% and 95% potency, respectively, compared with VEGF-A/VEGF-1). VEGF-C **stimulated** release of nitric oxide from endothelial cells and increased vascular permeability in the Miles assay; the latter effect was attenuated by pretreatment with the nitric...

...2 and VEGFR-3 receptors were shown to be expressed in human saphenous vein and internal mammary artery. The potential for VEGF-C to promote **angiogenesis** in vivo was then tested in a rabbit **ischemic** hindlimb model. Ten days after ligation of the external iliac artery, VEGF-C was administered as naked plasmid DNA (pcVEGF-C; 500 mug) from the...

...an angioplasty balloon (n=8 each) or as recombinant human protein (rhVEGF-C; 500 mug) by direct intra-arterial infusion. Physiological and anatomical assessments of **angiogenesis** 30 days later showed evidence of therapeutic **angiogenesis** for both pcVEGF-C and rhVEGF-C. Hindlimb blood pressure ratio (**ischemic** /normal) after pcVEGF-C increased to 0.83 +- 0.03 after pcVEGF-C versus 0.59 +- 0.04 ($P < 0.005$) in pGSVLacZ controls and...
...164 +- 20 ($P < 0.05$) for protein). in contrast to the results of gene targeting experiments, constitutive expression of VEGF-C in adult animals promotes **angiogenesis** in the setting of limb **ischemia** . VEGF-C and its receptors thus constitute an apparently redundant pathway for postnatal **angiogenesis** and may represent an alternative to VEGF-A for strategies of therapeutic **angiogenesis** in patients with limb and/or **myocardial ischemia** .
DESCRIPTORS:
DISEASES: **myocardial ischemia** -- **heart** disease, vascular disease
MESH TERMS: **Myocardial Ischemia** (MeSH...
...METHODS & EQUIPMENT: **imaging** method
MISCELLANEOUS TERMS: **angiogenesis** ;

John Sims EIC 3700 308-4836

Journal: ADVANCED DRUG DELIVERY REVIEWS, **1998** , V30, N1-3 (MAR 2), P 185-197
ISSN: 0169-409X Publication date: 19980302
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

Title: Arterial gene transfer of naked DNA for therapeutic angiogenesis **: early clinical results**
, **1998**
Abstract: Patients with critical limb ischemia constitute a potential target population for therapeutic **angiogenesis** , Because the growth of new collateral vessels can be achieved in a time interval of 1 month or less, these patients are suitable candidates for...
...extremity. Using a dose-escalating strategy, it was possible to document that naked DNA was sufficient to generate evidence of new collateral growth by both **magnetic resonance** angiography and contrast angiography in the affected limb. These findings establish that the use of naked DNA may be suitable for gene therapy when the...
...Identifiers--ENDOTHELIAL GROWTH-FACTOR; IN-VIVO; PERCUTANEOUS REVASCULARIZATION; **ISCHEMIC MYOCARDIUM** ; PROTEIN SECRETION; EXPRESSION; BALLOON; **INJURY;** INVIVO; MODEL

20/3,KWIC/4 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06653920 Genuine Article#: ZH422 No. References: 19
Title: Extent of myocardial collateralization: Determination with three-dimensional elastic-subtraction spiral CT
Author(s): Pearlman JD (REPRINT) ; Laham RJ; Simons M; Gladstone S; Raptopoulos V
Corporate Source: HARVARD UNIV,SCH MED, BETH ISRAEL DEACONESS MED CTR AN240, DEPT RADIOL, 330 BROOKLINE AV/BOSTON//MA/02215 (REPRINT); HARVARD UNIV,SCH MED, BETH ISRAEL DEACONESS MED CTR AN240, DEPT MED/BOSTON//MA/02215
Journal: ACADEMIC RADIOLOGY, **1997** , V4, N10 (OCT), P680-686
ISSN: 1076-6332 Publication date: 19971000
Publisher: ASSOC UNIV RADIOLOGISTS, 2021 SPRING RD, STE 600, OAK BROOK, IL 60521
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

, **1997**
Abstract: Rationale and objectives. This study was undertaken to develop a standard that can be used to assess new high-resolution collateral zone **imaging** methods.

Materials and Methods. The authors performed ex vivo helical CT in seven pig hearts after microsphere studies of blood flow and coronary angiography. They...

...was 6.5%, which indicates good agreement.

Conclusion. Accurate assessment of collateralization extent has become an important goal because of the discovery of agents that **stimulate** the growth of coronary collateral vessels. The precision of elastic-subtraction CT and its validation with respect to the blood flow distribution at microsphere analysis...
...Identifiers--FIBROBLAST GROWTH-FACTOR; BLOOD-FLOW; **ISCHEMIC MYOCARDIUM** ; CORONARY-OCCLUSION; **ANGIOGENESIS;** CIRCULATION;

INFARCTION; MODEL; DOG

20/3,KWIC/5 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06263928 Genuine Article#: YF058 No. References: 58
Title: Protection of rat myocardium **by mitogenic and non-mitogenic fibroblast growth factor during post-** ischemic **reperfusion**
Author(s): Cuevas P; Carceller F; Lozano RM; Crespò A; Zazo M; GimenezGallego G (REPRINT)
Corporate Source: CSIC,CTR INVEST BIOL, VELAZQUEZ 144/E-28006 MADRID//SPAIN/ (REPRINT); CSIC,CTR INVEST BIOL/E-28006 MADRID//SPAIN/; UNIV MADRID,HOSP RAMON Y CAJAL/MADRID 3//SPAIN/
Journal: GROWTH FACTORS, **1997** , V15, N1, P29-&
ISSN: 0897-7194 Publication date: 19970000
Publisher: HARWOOD ACAD PUBL GMBH, C/O STBS LTD, PO BOX 90, READING, BERKS, ENGLAND RG1 8JL
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Protection of rat myocardium **by mitogenic and non-mitogenic fibroblast growth factor during post-** ischemic **reperfusion**
, 1997
Abstract: The effects of acidic fibroblast growth factor (FGF-1) and basic fibroblast growth factor (FGF-2) and a non mitogenic form of FGF1 on **myocardial ischemia** and reperfusion were assessed. Rats underwent 10 minutes of coronary artery occlusion followed by 24 hours of reperfusion. Creatinine kinase content of the affected **myocardium** showed that both fibroblast growth factors 1 and 2 effectively protected against **ischemia** reperfusion **injury** ($p < 0.01$), and that the vasoactive but nonmitogenic form of the FGF1 was equally protective ($p < 0.01$ versus control + vehicle). The results were...

...form of the protein, also suggest that the protective effect of fibroblast growth factors may be due to the increased blood flow rather than to **angiogenesis** .
...Research Fronts: FACTOR BB; RESTENOSIS FOLLOWING CORONARY ANGIOPLASTY; RABBIT ARTERIES)
95-1848 001 (MYOCARDIAL VIABILITY; DOBUTAMINE STRESS ECHOCARDIOGRAPHY; CHRONIC CORONARY-ARTERY DISEASE; CLINICAL USE OF CARDIAC RADIONUCLIDE **IMAGING**)
95-8705 001 (**MYOCARDIAL** REPERFUSION **INJURY** ; ENDOTHELIAL NITRIC-OXIDE SYNTHASE; HYPOTHERMIC **ISCHEMIA** IN NEONATAL LAMB **HEARTS** ; CORONARY FLOW; L-ARGININE CARDIOPLEGIA)

20/3,KWIC/6 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06016974 Genuine Article#: XP599 No. References: 109
Title: Role of cytokines in myocardial ischemia **and reperfusion**
Author(s): Sharma HS (REPRINT) ; Das DK
Corporate Source: ERASMUS UNIV ROTTERDAM,DEPT PHARMACOL/NL-3000 DR ROTTERDAM//NETHERLANDS/ (REPRINT); UNIV CONNECTICUT,CTR HLTH, DEPT SURG/FARMINGTON//CT/
Journal: MEDIATORS OF INFLAMMATION, **1997** , V6, N3 (JUN), P175-183
ISSN: 0962-9351 Publication date: 19970600
Publisher: RAPID SCIENCE PUBLISHERS, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1

8NH
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

Title: Role of cytokines in myocardial ischemia **and reperfusion , 1997**

Abstract: Mediators of **myocardial** inflammation, predominantly cytokines, have for many years been implicated in the healing processes after infarction. In recent years, however, more attention has been paid to the possibility that the inflammation may result in deleterious complications for **myocardial** infarction. The proinflammatory cytokines may mediate **myocardial** dysfunction associated with **myocardial** infarction, severe congestive **heart** failure, and sepsis. A growing body of literature suggests that inflammatory mediators could play a crucial role in **ischemia** -reperfusion **injury** . Furthermore, **ischemia** -reperfusion not only results in the local transcriptional and translational upregulation of cytokines but also leads to tissue infiltration by inflammatory cells. These inflammatory cells...

...metabolism and subsequent irreversible cell membrane damage leading to cell death. For instance, hypoxic cardiomyocytes produce interleukin-6 (IL-6) which could contribute to the **myocardial** dysfunction observed in **ischemiareperfusion injury** . **Ischemia** followed by reperfusion induces a number of other multi-potent cytokines, such as IL-1, IL-8, tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-alpha (TGF-beta 1) as well as an angiogenic cytokine/ growth factor, vascular endothelial growth factor (VEGF), in the **heart** . Intrestingly, these multipotent cytokines (e.g. TNF-alpha) may induce an adaptive cytoprotective response in the reperfused **myocardium** . In this review, we have included a number of cytokines that may contribute to ventricular dysfunction and/or to the cytoprotective and adaptive changes in the reperfused **heart** .

...Research Fronts: POEMS SYNDROME; GIANT LYMPH-NODE HYPERPLASIA; MYELOMA CELLS)

95-1848 001 (MYOCARDIAL VIABILITY; DOBUTAMINE STRESS ECHOCARDIOGRAPHY; CHRONIC CORONARY-ARTERY DISEASE; CLINICAL USE OF CARDIAC RADIONUCLIDE **IMAGING**)

95-2892 001 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; TUMOR **ANGIOGENESIS** ; COORDINATE EXPRESSION)

95-3685 001 (CARDIOPULMONARY BYPASS; ARTIFICIAL SURFACES DEMONSTRATES REDUCED COMPLEMENT ACTIVATION; CIRCULATING ADHESION MOLECULES IN CARDIAC OPERATIONS)

95-7159 001 (HUMAN THYMIDINE KINASE...

20/3,KWIC/7 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05836444 Genuine Article#: XA653 No. References: 13

Title: Harmonic imaging **of porcine intraovarian arteries using sonographic contrast medium initial findings**

Author(s): Ragavendra N (REPRINT) ; Chen H; Powers JE; Nilawat C; Robert JM ; Carangi C; LaiferNarin SL

Corporate Source: 300 UCLA MED PLAZA,SUITE 3102/LOS ANGELES//CA/90095 (REPRINT); UNIV CALIF LOS ANGELES,SCH MED, DEPT RADIOL SCI/LOS ANGELES//CA/90024

Journal: ULTRASOUND IN OBSTETRICS & GYNECOLOGY, **19**97 , V9, N4 (APR), P 266-270

ISSN: 0960-7692 Publication date: 19970400

Publisher: PARTHENON PUBLISHING GROUP, CASTERTON HALL, CARNFORTH

John Sims EIC 3700 308-4836

LANCASHIRE, ENGLAND LA6 2LA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Harmonic imaging **of porcine intraovarian arteries using sonographic contrast medium initial findings**
, **1997**
Abstract: The purpose of this study teas to visualize, using harmonic gray-scale **imaging** , blood flow in porcine intraovarian arteries after intravenous injections of a bubble-based sonographic contrast medium. Five female pigs underwent laparotomy. Surgically isolated ovaries were scanned intraperitoneally by an ultrasound system reconfigured with software changes to accomplish harmonic **imaging** . The transmission and receiving frequencies were set at 3.75 and 7.5 MHz, respectively. After injection of the sonographic contrast medium (Aerosomes(R)) into a peripheral vein, the ovaries were imaged in the harmonic mode. Ten minutes later, another contrast injection was administered and conventional gray-scale **imaging** of the ovary performed. In all five pigs, intraovarian arteries were clearly identified upon harmonic **imaging** as brightly echogenic moving columns. The arterial blood pool appeared brighter during systole than diastole. Upon ultrasound contrast-assisted conventional gray-scale **imaging** , intraovarian arteries were not visualized in four pigs and poorly visualized in one. We conclude that contrast-assisted harmonic **imaging** can adequately visualize blood flow in intraovarian arteries of surgically exposed porcine ovaries. Clinically, harmonic **imaging** may facilitate early detection of tumor-induced **angiogenesis** in the human ovary.
Research Fronts: 95-5489 001 (**MYOCARDIAL** CONTRAST ECHOCARDIOGRAPHY; **ISCHEMIA** -REPERFUSION **INJURY** ; CANINE MODEL; CORONARY MICROCIRCULATION)

20/3,KWIC/8 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05284259 Genuine Article#: VM749 No. References: 59
Title: GENE-TRANSFER OF NAKED DNA ENCODING FOR 3 ISOFORMS OF VASCULAR ENDOTHELIAL GROWTH-FACTOR STIMULATES **COLLATERAL DEVELOPMENT IN-VIVO**
Author(s): TAKESHITA S; TSURUMI Y; COUFFINAHL T; ASAHARA T; BAUTERS C; SYMES J; FERRARA N; ISNER JM
Corporate Source: TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT MED CARDIOL,736 CAMBRIDGE ST/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT MED CARDIOL/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT CARDIOVASC SURG/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT BIOMED RES/BOSTON//MA/02135; GENENTECH INC,DEPT CARDIOVASC RES/S SAN FRANCISCO//CA/94080
Journal: LABORATORY INVESTIGATION, **1996** , V75, N4 (OCT), P487-501
ISSN: 0023-6837
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: GENE-TRANSFER OF NAKED DNA ENCODING FOR 3 ISOFORMS OF VASCULAR ENDOTHELIAL GROWTH-FACTOR STIMULATES **COLLATERAL DEVELOPMENT IN-VIVO**
, **1996**
...Abstract: endothelial cell-specific mitogen. We investigated the hypothesis that naked DNA encoding for VEGF could be used in a strategy of arterial gene therapy to **stimulate** collateral artery development. Plasmid DNA encoding each of the three principal human VEGF isoforms (phVEGF(121), phVEGF(165), or phVEGF(189)) was applied to the...

...Similar results were obtained with phVEGF(121), phVEGF(165), and

phVEGF(189), which suggests that these isoforms are biologically equivalent with respect to in vivo **angiogenesis** . The fact that viral or other adjunctive vectors were not required further suggests that secreted gene products may have potential therapeutic utility even when the...

...cells remains low. Arterial gene transfer of naked DNA encoding for a secreted angiogenic cytokine, thus, represents a potential alternative to recombinant protein administration for **stimulating** collateral vessel development.
...Identifiers--IN-VIVO; THERAPEUTIC **ANGIOGENESIS** ; CELLULAR PROLIFERATION; **ISCHEMIC MYOCARDIUM** ; PROTEIN SECRETION; RABBIT MODEL; TIME-COURSE; EXPRESSION; INVIVO; ARTERY
Research Fronts: 94-5407 002 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; CORONARY **ANGIOGENESIS** ; WILD-TYPE P53 EXPRESSION IN GLIOBLASTOMA CELLS)
94-0253 001 (PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY; PROSPECTIVE RANDOMIZED TRIAL FOR ARTERIAL PUNCTURE SITE CLOSURE; PREDICTING ISCHEMIC COMPLICATIONS)
94-0785 001 (INTRAVASCULAR ULTRASOUND **IMAGING** ; POSTSTENOTIC CORONARY FLOW RESERVE; UNSTABLE ANGINA)
94-8400 001 (DIRECT DNA INJECTION; VACCINE DELIVERY; IN-VIVO GENE-TRANSFER; PROTECTIVE IMMUNITY; NUCLEIC-ACID IMMUNIZATION; SKELETAL-MUSCLE...

20/3,KWIC/9 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03547673 Genuine Article#: PL936 No. References: 27
Title: SELECTIVE CLOSURE OF THE VASCULAR BED OF AN EXPERIMENTAL GLIOMA MODEL DURING IN-SITU SALINE PERFUSION
Author(s): LUTHERT PJ; GREENWOOD J
Corporate Source: INST OPHTHALMOL,DEPT PATHOL,BATH ST/LONDON EC1V9EL//ENGLAND/; INST PSYCHIAT,DEPT NEUROPATHOL/LONDON SE5 8AF//ENGLAND/
Journal: NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY, **1994** , V20, N5 (OCT), P 448-453
ISSN: 0305-1846
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

, **1994**
...Identifiers--EXPERIMENTAL BRAIN-TUMORS; BLOOD-FLOW; RAT-BRAIN; PERMEABILITY; BARRIER; **ANGIOGENESIS;** CHEMOTHERAPY; TRANSPORT; TISSUE; LIGHT
Research Fronts: 92-0789 001 (**MYOCARDIAL** REPERFUSION **INJURY** ; REACTIVE OXYGEN INTERMEDIATES; GASTRIC INTRAMUCOSAL PH; COLD **ISCHEMIA**)
92-2388 001 (**POSITRON EMISSION TOMOGRAPHY** ; 3-DIMENSIONAL FUNCTIONAL BRAIN IMAGES; REGIONAL CEREBRAL BLOOD-FLOW)
92-5511 001 (TUMOR **ANGIOGENESIS** ; FIBROBLAST GROWTH-FACTOR; ANTIANGIOGENIC AGENTS)

20/3,KWIC/10 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06276632 EMBASE No: 1995302287
Magnetic resonance **mapping demonstrates benefits of VEGF-induced**

myocardial angiogenesis

Pearlman J.D.; Hibberd M.G.; Chuang M.L.; Harada K.; Lopez J.J.; Gladstone S.R.; Friedman M.; Sellke F.W.; Simons M.
Department of Radiology, Harvard Medical School, Beth Israel Hospital,Boston, MA 02215 United States

Nature Medicine (NAT. MED.) (United States) 1995, 1/10 (1085-1089)
CODEN: NAMEF ISSN: 1078-8956
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Magnetic resonance **mapping demonstrates benefits of VEGF-induced myocardial** angiogenesis

...infarction because they have sufficient collateral vessels providing an alternate pathway for blood supply. Vascular endothelial growth factor (VEGF) is an angiogenic peptide that can **stimulate** collateral vessel development in the ischaemic myocardium. We used **magnetic resonance imaging** (**MRI**) and image processing to identify and quantify non-invasively the benefits related to VEGF infusion on collateral development in the heart. This was accomplished as...

MEDICAL DESCRIPTORS:
* **angiogenesis** ; *coronary artery collateral circulation; *heart infarction --prevention--pc; *heart infarction--drug therapy--dt; * **heart** muscle **ischemia**
animal experiment; animal model; article; controlled study; intracardiac drug administration; nonhuman; nuclear **magnetic resonance imaging** ; priority journal; swine
1995
?

DIALOG(R)File 5:Biosis Previews(R)

0006211583 BIOSIS NO.: 198886051504
IMPROVEMENT OF TREADMILL CAPACITY AND COLLATERAL CIRCULATION AS A RESULT OF EXERCISE WITH HEPARIN PRETREATMENT IN PATIENTS WITH EFFORT ANGINA
AUTHOR: FJUITA M (Reprint); SASAYAMA S; ASANOI H; NAKAJIMA H; SAKAI O; OHNO A
AUTHOR ADDRESS: SECOND DEP INTERNAL MED, TOYAMA MED PHARM UNIV, 2630 SUGITANI, TOYAMA 930-01, JPN**JAPAN
JOURNAL: Circulation 77 (5): p1022-1029 1988
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

...ABSTRACT: the above-mentioned variables of treadmill capacity remained unchanged, despite 20 exercise periods without heparin pretreatment. Thus, heparin accelerates exercise-induced coronary collateral development by **promoting angiogenesis** . The development of such a therapeutic modality will open a new field for the treatment of patients with ischemia.

11/3,KWIC/5 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03543731 Genuine Article#: PL505 No. References: 81
Title: CLINICAL-SIGNIFICANCE OF CORONARY VASCULAR ADAPTATIONS TO EXERCISE TRAINING
Author(s): MCKIRNAN MD; BLOOR CM
Corporate Source: UNIV CALIF SAN DIEGO,SCH MED,DEPT PATHOL,0612,9500 GILMAN DR/LA JOLLA//CA/92093; UNIV CALIF SAN DIEGO,SCH MED,DEPT PATHOL/LA JOLLA//CA/92093
Journal: MEDICINE AND SCIENCE IN SPORTS AND EXERCISE, 1994, V26, N10 (OCT) , P1262-1268
ISSN: 0195-9131
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: ischemia and measuring myocardial blood now and the variability in exercise stimulus. Well-established ischemia and high-intensity, long-duration training were the factors that **promoted** vascular growth in exercising patients with coronary artery disease. Animals studies also have demonstrated the necessity for myocardial ischemia to be present to induce coronary collateral development with exercise training. Optimal **promoters** of vascular growth in patients with coronary disease may consist of pharmacological interventions combined with exercise training.
...Identifiers--LEFT-VENTRICULAR FUNCTION; HIGH-INTENSITY **EXERCISE** ; COLLATERAL BLOOD-FLOW; ARTERY DISEASE; MYOCARDIAL **PERFUSION** ; HEART-DISEASE; ANGINA-PECTORIS; PHYSICAL-ACTIVITY; CARDIAC REHABILITATION; PLASMA CATECHOLAMINES

11/3,KWIC/6 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03396344 Genuine Article#: PB893 No. References: 31

92-2715 001 (INSULIN SENSITIVITY IN MUSCLE; **PERFUSIVE** O2 TRANSPORT DURING **EXERCISE** ; DIAPHRAGMATIC FIBERS)

11/3,KWIC/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

12114745 EMBASE No: 2003227993
Enhanced external counterpulsation for ischemic heart disease: What's behind the curtain?
Bonetti P.O.; Holmes Jr. D.R.; Lerman A.; Barsness G.W.
Dr. G.W. Barsness, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 United States
AUTHOR EMAIL: barsness.gregory@mayo.edu
Journal of the American College of Cardiology (J. AM. COLL. CARDIOL.) (United States) 04 JUN 2003, 41/11 (1918-1925)
CODEN: JACCD ISSN: 0735-1097
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 66

...patients with refractory angina. Prospective clinical studies and large treatment registries suggest that a course of EECP is associated with prolongation of the time to **exercise** -induced ST-segment depression and resolution of myocardial **perfusion** defects, as well as with enhanced **exercise** tolerance and quality of life. With a growing knowledge base supporting the safety and beneficial clinical effects associated with EECP, this therapy can be considered...
...the mechanisms responsible for the beneficial effects associated with this technique. Suggested mechanisms contributing to the clinical benefit of EECP include improvement in endothelial function, **promotion** of coronary collateralization, enhancement of ventricular function, peripheral effects similar to those observed with regular physical **exercise** , and nonspecific placebo effects. This review summarizes the current evidence for a contribution of these mechanisms to the clinical benefit associated with EECP. (c) 2003...
MEDICAL DESCRIPTORS:
...perfusion; stable angina pectoris--therapy--th; cardiovascular risk; oxidative stress; coronary artery dilatation; coronary artery blood flow; collateral circulation; peripheral circulation; protein induction; protein function; **angiogenesis** ; coronary artery collateral circulation; heart left ventricle function; exercise test; positron emission tomography; validation process; outcomes research; human; review; priority journal

11/3,KWIC/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

11387014 EMBASE No: 2001401563
Therapeutic angiogenesis **in critical limb and myocardial ischemia**
Vale P.R.; Isner I.M.; Rosenfield K.
Dr. K. Rosenfield, St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA 02135 United States
AUTHOR EMAIL: krosenfield@pol.net
Journal of Interventional Cardiology (J. INTERVENT. CARDIOL.) (United States) 2001, 14/5 (511-528)
CODEN: JICAF ISSN: 0896-4327
DOCUMENT TYPE: Journal ; Conference Paper